EFFECT OF SUPERDISINTEGRANTS ON ORAL DISINTEGRATING TABLETS OF ZOLMITRIPTAN

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

Chennai-600032

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted by

Register No. 261210603

Under the Guidance of

Prof. R. NATARAJAN, M. PHARM., (Ph.D).

DEPARTMENT OF PHARMACEUTICS

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY

ELAYAMPALAYAM, TIRUCHENGODE - 637 205

TAMILNADU.

APRIL-2014

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY
Elayampalayam, Tiruchengode - 637 205
Namakkal (DT), Tamilnadu.
Phone: 04288-234417(8 lines)
Fax: 04288-234417

Dr. N. N. RAJENDRAN, M. PHARM., PH. D.
Principal

CERTIFICATE

This is to certify that the dissertation entitled **"EFFECT OF SUPERDISINTEGRANTS ON ORAL DISINTEGRATING TABLETS OF ZOLMITRIPTAN"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, is a bonafide project work of **(Reg. No: 261210603)** in the Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy, Tiruchengode, for the partial fulfillment of award of the degree in Master of Pharmacy under the guidance of **Prof. R. NATARAJAN, M.Pharm., (Ph.D).** Swamy Vivekanandha College of Pharmacy, Tiruchengode.

Signature of Principal
Dr. N. N. Rajendran, M. Pharm., Ph. D.

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY
Elayampalayam, Tiruchengode - 637 205
Namakkal (DT), Tamilnadu.
Phone: 04288-234417(8 lines)
Fax: 04288-234417

Dr. N. N. RAJENDRAN, M. PHARM., PH. D.
Director of P.G. Studies and Research

CERTIFICATE

This is to certify that the dissertation entitled **"EFFECT OF SUPERDISINTEGRANTS ON ORAL DISINTEGRATING TABLETS OF ZOLMITRIPTAN"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, is a bonafide project work of **(Reg. No: 261210603)** in the Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy, Tiruchengode, for the partial fulfillment of award of the degree in Master of Pharmacy under the guidance of **Prof. R. NATARAJAN, M.Pharm., (Ph.D).** Swamy Vivekanandha College of Pharmacy, Tiruchengode.

Signature of Director of P.G. Studies and Research
Dr. N. N. Rajendran, M. Pharm., Ph. D.

SWAMY VIVEKANANDHA COLLEGE OF PHARMACY
Elayampalayam, Tiruchengode - 637 205
Namakkal (DT), Tamilnadu.
Phone: 04288-234417(8 lines)
Fax: 04288-234417

Prof. R.NATARAJAN, M.PHARM.,(Ph.d).,
Head and department of pharmaceutics

CERTIFICATE

This is to certify that the dissertation entitled **"EFFECT OF SUPERDISINTEGRANTS ON ORAL DISINTEGRATING TABLETS OF ZOLMITRIPTAN"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, is a bonafide project work of **(Reg.No:261210603),** in the Department of Pharmaceutics, Swamy Vivekanandha College of Pharmacy, Tiruchengode, for the partial fulfillment of award of the degree in Master of Pharmacy under my supervision & guidance.

This work has not been submitted in part or full for the award of any degree or diploma of this or any other university.

Signature of the Guide
R.NATARAJAN, M.PHARM.,(Ph.D)

ACKNOWLEDGEMENT

Behind every successful venture, it is always said that there is an invisible force, which shapes the things in the right way and directions in which they should be. I found it moral duty to bow to that divine power and thank him for imbibing in me the strength required for the successful completion of the thesis work.

Ability and ambition are not enough for success many an able person fails to achieve anything worthwhile because he has not been properly guided. Success of any project depends solely on support, guidance and encouragement received from the guide and well-wishers.

It is with a sense of pride and pleasure that, I humbly look back to acknowledge, those who have been a source of encouragement in my entire endeavor.

Many Thanks to Almighty**,** for it is He who began this work in me and carried it throughout completion.

The completion of this dissertation is not only fulfillment of my dreams but also the dreams of my Parents, who have taken lots of pain for me in completion of my higher studies.

I take this privilege and pleasure to acknowledge the contributions of many individuals who have been inspirational and supportive throughout my work undertaken and endowed me with the most precious knowledge to see success in my endeavor. My work bears the imprint of all those people.

We submit our sincere thanks to our beloved chairman and secretary "Vidya Ratna, Rashtriya Rattan, Hind Ratna" **Prof. Dr. M. KARUNANITHI, B.Pharm, M.S., Ph.D., D. Litt.** for providing all the facilities to carry out this thesis work.

It gives me great pleasure to record my deep sense of gratitude and indebtedness to **Prof**. **R.NATARAJAN, M.Pharm.,(Ph.D).,** Prof & Head., Department of Pharmaceutics , whose guidance, support, critical evaluations and professional eminency have inspired me a lot to put optimum efforts towards the completion of my thesis work.

I consider it is a great honor to express my deep sense of gratitude and indebtedness to **Dr. N. N. RAJENDRAN, M.Pharm., Ph.D.,** Director of P.G.Studies and Research, Swamy Vivekanandha College of Pharmacy, for his valuable suggestion throughout the course of investigation and successful completion of the work.

I also take this opportunity to express my deep sense of gratitude and offer my most sincere and humble regards to Prof**, Mr.K.MOHAN KUMAR, M.PHARM,** Department of Pharmaceutics, for his continuous encouragement and support in completion of my course and dissertation successfully.

It would be unwise if I forget to express my sincere thanks and gratitude to **Mrs. M. RANGA PRIYA, M. Pharm., (Ph. D)** Asst.Professor, Department of Pharmaceutics for his valuable help, support and encouragement during the work.

I am elated to place on record my profound sense of gratitude **Mrs. R. SUBHASHINI M. Pharm.,** Asst. professor, Department of Pharmaceutics, for his timely help during the work.

Good friends are gift of God! I express my deep sense of gratitude and love towards my friends, well wishers and all my batch mates.

I would like to express my sincere thanks to **Mr**. **S**. **MOHAMADH (M.PHARM), Mr. M. MURUGAN (M.PHARM), Mr. C. KRISHNAN (M. PHARM)** providing constant source of inspiration and has always encouraged scientific thinking and instilled me a sense of discipline in my work.

I express my deep sense of gratitude and love to my father **CH. VENKATESWARLU** for timely help throughout the study without his support I wouldn't have reached this place, my love and gratitude to my beloved Mother **CH. PADMAWATHI,** from depth of my heart for giving me more than what I deserved. It gives me an immense pleasure to dedicate my research work at their feet without whose blessings and vision. I would not have been able to achieve this task.

I pay tribute to my beloved family for lifting me up till this phase of life. I thank them for their love, trust, patience and support and bearing all kinds of stress to make me what am.

I would like to express my sincere thanks to **MISS LATHA (BSC.MATHS),** for their help and support in all my laboratory tests.

I would like to thank all those who have helped me directly or indirectly to complete this work successfully.

Ch.Sravanthi

Reg.no:261210603

CONTENTS

ABSTRACT

Orally disintegrating tablets (ODTs) are getting popularity over conventional tablets due to their convenience in administration and suitability for patients having dysphagia (difficulty in swallowing). There is an increasing demand for more patient compliance dosage form and a novel method is the development orally disintegrating tablets which dissolve or disintegrates instantly on the patient tongue or buccal mucosa. It is suited for tablets undergoing high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to minimize side effect and make it more cost effective. Zolmitriptan is a selective serotonin receptor agonist. The absolute bioavailability is only approximately 40% due to extensive hepatic first pass metabolism (CYP1A2-mediated). Hence the main objective of the study was to formulate oral disintegrating tablets of Zolmitriptan to achieve a better dissolution rate and further improving the bioavailability of the drug. Orally disintegrating tablets prepared by direct compression and using, Crosspovidone, Crosscarmellose sodium, Sodium starch glycolate, Mannitol ,Magnesium stearate, Talc, Aerosil, Citric acid were prepared and evaluated for the precompression parameters such as bulk density, tapped density, compressibility index , angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, disintegration time and in-vitro dissolution profile and found satisfactory. Among these groups, F6 Formulation is the best formulation and showed maximum dissolution rate with drug release within 10 minutes (94.4%) and it containing Crosspovidone as a superdisintegrant showed minimum disintegration time 15 seconds.

1. INTRODUCTION

Oral disintegration tablets are the novel technology for administration of the drug through the oral route. The tablet is the most widely used dosage form because of its convenience in terms of self -administration, compactness and ease in manufacturing. However, many patients especially children and elderly have difficulty in swallowing tablets and capsules and consequently unable to take medicine as prescribed. Almost 50% of the population is affected by such problem, resulting in the high incidence of non compliance and infective therapy. To overcome such problems, fast disintegrating tablets or orally disintegrating tablets have emerged as an alternative dosage forms.

Oral disintegrating tablets's are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. An Oral disintegration tablets is a solid dosage form that disintegrates and dissolves in the mouth without water within 60 seconds or less. Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. ODTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.

A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue."Orally disintegrating tablets have been found to be the choice for Psychiatric as well as patient suffering from stroke, thyroid disorder, Parkinson's diseases and multiple sclerosis, patients with nausea, vomiting and motion sickness. These systems are also called melt-in-mouth tablets, Rapid melts, porous tablets, Oro dispersible, quick dissolving or rapidly disintegrating tablets [1-7].

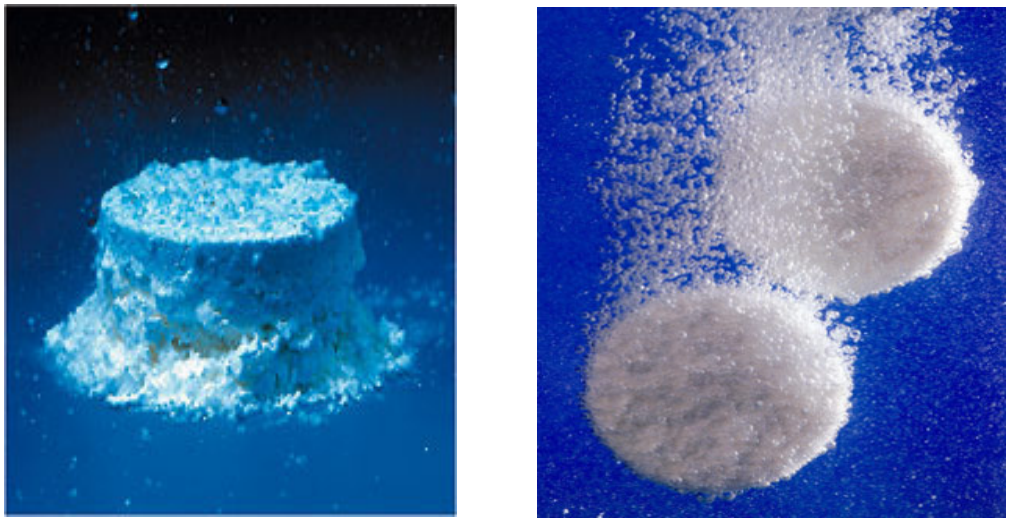


Fig.1 oral disintegrating tablets

In today's era many people are suffering from migraine. Migraine is a one sided throbbing headache followed by neurological and visual disturbances. Attack may prolong for long period. Patients routinely report the pain of an attack as being the most severe they have ever experienced, or Migraine is often disabling neurovascular disorder. Changes in the metabolism and the central processing of serotonin, as well as abnormalities in the modulation of the central and peripheral trigeminal nociceptive pathways, have been shown to play significant roles in migraine pathophysiology. Recent evidence suggests that a low serotonin state facilitates activation of the trigeminal nociceptive pathways. In addition, several pharmacological agents that modulate serotonin are used in the treatment of migraine. Specifically there are seven FDA approved, 5-hydroxytryptamine (5-HT) 1B/1D receptor agonists, used for the acute abortive therapy of migraine. Zolmitriptan is one such triptan.

Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea and photo or photophobia. It is currently available as a conventional tablet, an oral disintegrating tablet and a nasal spray (2.5 mg and 5 mg) per dose. The absolute bioavailability of zolmitriptan is up to (40%- 50%) for both oral and nasal dosage forms. The faster clearance of the drug from the nasal cavity could explain the low bioavailability. The half-life of the Zolmitriptan is 2.5 to 3 hrs and it undergoes hepatic metabolism. In the present study we intend to prepare oral disintegrating tablet

of Zolmitriptan (2.5 mg) in order to improve the bioavailability and efficacy by using Crosscarmellose sodium, Sodium starch glycolate, Crosspovidone as disintegrates. Recent developments in technology have presented viable dosage alternatives for pediatric, geriatric, bedridden, nauseous or non-compliant patients, who face difficulty in swallowing or chewing solid dosage forms and are unwilling to take solid preparations due to a fear of choking. Hence, mouth dissolving/disintegrating tablets are a perfect fit for them. Super disintegrates added in the formulation increase the drug release, thus increasing the bioavailability of drug. Mouth disintegrating tablets when placed in the mouth, disintegrate instantaneously, releasing the drug, which dissolves or disperses in the saliva and can be swallowed as a liquid, without the aid of water. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than that observed from conventional tablet dosage form. This system of drug delivery allows children, elderly, and the general population to take their medications discretely wherever and whenever needed, much eliminating the factor of patient non-compliance. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make these tablets popular as a dosage form of choice in the current market [(8)].

1.1 Oral Disintegrating Tablets

Dysphasia or difficulty in swallowing is common among all age groups. According to studies dysphagia is common in about 35% of general population.

Common complaints about difficulty in swallowing tablets

- Size
- Surface
- Form
- Taste of tablets

Definition

An *ODT* is a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity without water within 60 seconds or less. The US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines an ODT as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue. [8]

The European Pharmacopoeia however defines a similar term, oro-disperse, as a tablet that can be placed in the mouth where it disperses rapidly before swallowing. [9]

Advantanges [10]:

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.

- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets.

  Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bio availability.

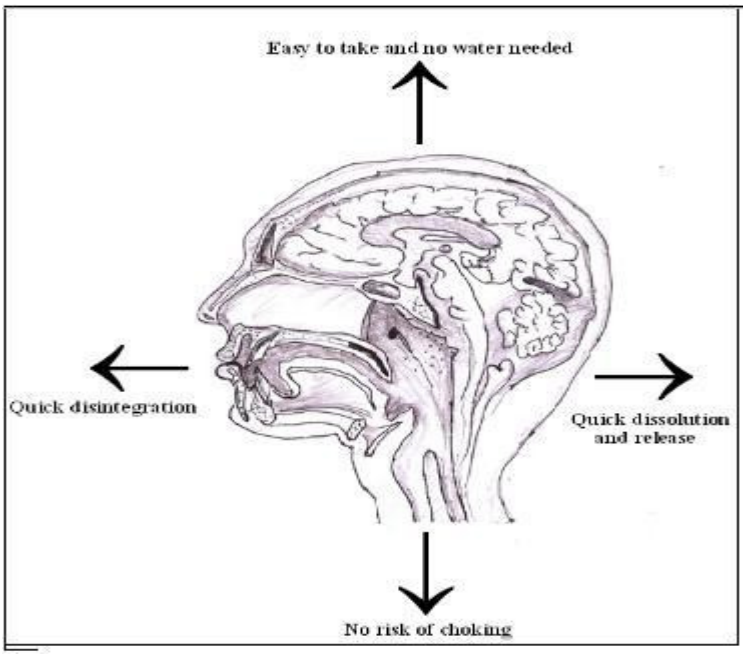


Fig 2 showing advantages of ODTs

Ideal Characteristics of Oral disintegration tablets. [11,12]

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include (Kuchekar et al, 2003).

1. No water requirement for swallowing purpose but it should dissolve or disintegrate in the mouth usually within fraction of seconds.

2. Provide pleasant feeling in the mouth.

3. Be compatible with taste masking.

4. Be portable without fragility concern.

5. Leave negligible or no residue in the mouth after oral administration.

6. Exhibit low sensitivity to altered environmental conditions such as humidity and temperature.

7. Allow high drug loading.

8. Adaptable and amenable to conventional processing and packaging equipment at nominal expense

.

Various approaches employed in manufacture of Oral disintegrating tablets:

There are number of techniques generally employed in the formulation of orally disintegrating dosage forms. These techniques have their own advantages as well as disadvantages and are described below:

a) Freeze-drying [13].

This method is suitable for thermolabile drugs, since it does not employ heat in the manufacturing process. It is a process in which water is sublimated from the product after freezing. The product prepared using this method is highly porous and has a very high specific surface area, which dissolves rapidly when in contact with water [11, 19-20]. The disadvantages of this method besides producing fragile products, are the use of high cost equipment and complex processing steps, which limit the use of this method.

(b) Tablet moulding [14,15].

Tablet moulding method uses water-soluble ingredients so that the tablets dissolve completely andrapidly. Moulding process includes moistening, dissolving, or dispersing of drug with a solvent. The powder blend is then moulded into tablets under pressure lower than that used in conventional tablet compression. Air drying process removes the solvent in the tablet. As a result, moulded tablets are very porous and less compact than compressed tablets. The ODT possesses porous structure that improves dissolution.

(c) Sublimation [16]

Sublimation is a manufacturing method which produces porous ODT with fast disintegration. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate and camphor) are mixed with other tablet ingredients and the mixture is compressed into tablets. When the volatile materials are sublimated, an ODT with porous structures is produced . Kizumi et al. (1997) developed ODT utilizing camphor as subliming material. Camphor was sublimated in vacuum at 800C for 30 min after preparation of tablets. Hence, the tablet produced is highly porous with fast disintegration time.

(d).Direct compression [16]

Direst compression is the easiest and conventional way to manufacture ODT. The advantages of this method are low manufacturing cost, the use of conventional equipments and limited number of processing steps. However, the disintegration and dissolution of the ODT are slower due to the more compacted and less porous ODT formed. The disintegration of ODT manufactured using this method was dependent on Superdisintegrant, water soluble excipients and effervescing agents.

(e) Spray drying [17]

Spray drying technique produces highly porous and fine powders as the processing solvent is evaporated during this process. However, this method is not suitable for heat sensitive drugs. ODT manufactured using this method disintegrates within 20 seconds when immersed in an aqueous medium. Allen and Wang (1993) reported an example of ODT manufactured using this method [23]. Hydrolyzed and non-hydrolyzed gelatin were used as supporting matrix, mannitol as bulking agent, sodium starch glycolate as superdisintegrant, citric acid and sodium bicarbonate as

disintegration and dissolution enhancers.

(f) Mass extrusion

Mass extrusion involves softening of the active blend using a solvent mixture of water-soluble polyethylene glycol and methanol, and subsequent expulsion of soft mass through an extruder. The product is cut into even segment using heating blade. The dried cylinder can also be used to coat granules of bitter tasting drugs and there by masking their bitter taste.

(g) Phase transition [18].

Two sugar alcohols, one with high and one with low melting points are used to manufacture ODT. The ODT is compressed then heated at a temperature between the melting points of the two sugar alcohols. The tablet hardness was increased after heating process, due to increase of inter-particle or the bonding surface area in the tablets induced by phase transition of lower melting point sugar alcohol

Superdisintegrants

Disintegrants are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of dosage form in dissolution fluids. An oral solid dosage form should ideally disperse into the primary particles from which it was prepared . Superdisintegrants are generally used at a low concentration, typically 1-10% by weight relative to total weight of dosage unit. Generally employed superdisintegrants are croscarmellose sodium (Ac-Di-Sol), crospovidone (CP), sodium starch glycolate (SSG) etc. which represent example of crosslinked cellulose, crosslinked polymer and crosslinked starch respectively. Selection of appropriate formulation excipients and manufacturing technology is necessary for obtaining the optimized design features of orally disintegrating dosage forms. Ideally, superdisintegrants should cause the tablet to disrupt, not only into the granules from which it was compressed but also into powder particles from which the granules were prepared.

Selection of superdisintegrants [19]:

Although superdisintegrants primarily affect the rate of disintegration, but when used at high

levels they can also affect mouth feel, tablet hardness and friability. Hence, various ideal factors to be considered while selecting an appropriate Superdisintegrants for a particular formulation should contain

1. Produce rapid disintegration, when tablet comes in contact with saliva in the mouth/oral cavity.
2. Be compactable enough to produce less friable tablets.
3. Produce good mouth feel to the patients. Thus, small particle size is preferred to achieve patient compliance.
4. Have good flow, since it improves the flow characteristics of total blend.

Mechanism of action of disintegrant. [20,21,22,]

Various mechanisms proposed in this concern include water wicking, swelling, deformation recovery, repulsion and heat of wetting. It seems likely that no single mechanism can explain the complex behavior of the disintegrants. However, each of these proposed mechanisms provides some understanding of different aspects of disintegrant action.

Water wicking

The ability of disintegrant to draw water into the porous network of tablet is essential for effective disintegration. On keeping the tablet into suitable aqueous medium, the medium enters into tablet and replaces the air adsorbed on the particles which weakens the intermolecular bonds and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipients and on tableting conditions. Unlike swelling, which is mainly a measure of volume expansion with accompanying force generation, water wicking is not necessarily accompanied by a volume increase. The ability of a system to draw water can be summarized by Washburn's equation:

$$L2 = (\gamma \, Cos\theta/2\eta) \times rt$$

The Washburn equation is too simplistic to apply to a dynamic tablet-disintegration process, but it does show that any change in the surface tension (γ), pore size (r), solid-liquid contact angle (θ) or liquid viscosity (η) could change the water wicking efficiency. L is the length of water penetration in the capillary and t is the time. This process is also considered as capillary action method.

Swelling

Although water penetration is a necessary first step for disintegration, swelling is probably the most widely accepted mechanism of action for tablet disintegrants. For swelling to be effective as a mechanism of disintegration, there must be a superstructure against which disintegrants swells. Figure 2 represents the disintegration of tablet by wicking and swelling. Swelling of the disintegrant against the matrix leads to development of a swelling force. A large internal porosity in the dosage form in which much of the swelling can be accommodated reduces the effectiveness of the disintegrant. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slowed down.

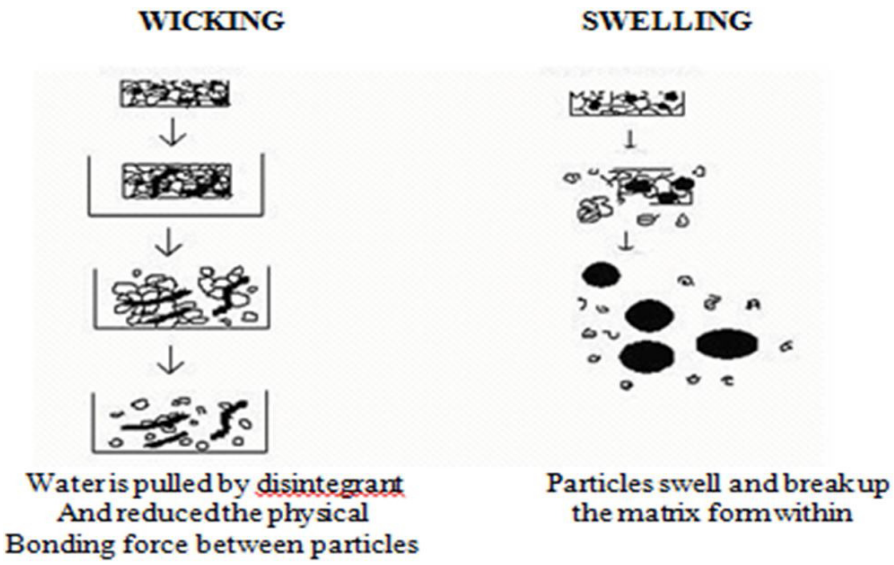


Fig.3 Disintegration of Tablet by Wicking and Swelling

Heat of wetting

When disintegrants with exothermic properties get wetted, localized stress is created due to capillary air expansion, which aids in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

Due to release of gases

Carbon dioxide gets released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during preparation of the tablets. The effervescent blend is either added immediately prior to compression or can be added into two separate fractions of formulation.

Particle repulsive forces

This is another mechanism of disintegration that attempts to explain the swelling of tablet made with non-swellable disintegrants. Guyot-Hermann proposed a particle-particle repulsion theory to explain the observation that particles which do not swell extensively such as starch, could still disintegrates tablets. According to this theory, water penetrates into tablet through hydrophilic pores and a continuous starch network is created that can convey water from one particle to the next, imparting a significant hydrostatic pressure. The water then penetrates between starch grains because of its affinity for starch surfaces, thereby breaking hydrogen bonds and other forces holding the tablet together. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

Deformation recovery

Deformation recovery theory implies that the shape of disintegrant particles is distorted during compression and the particles return to their precompression shape upon wetting, thereby causing the tablet to break apart. Such a phenomenon may be an important aspect of the

mechanism of action of disintegrants such as crospovidone and starch that exhibit little or no swelling. Disintegration of tablet by deformation as well as repulsion is illustrated in Figure 3

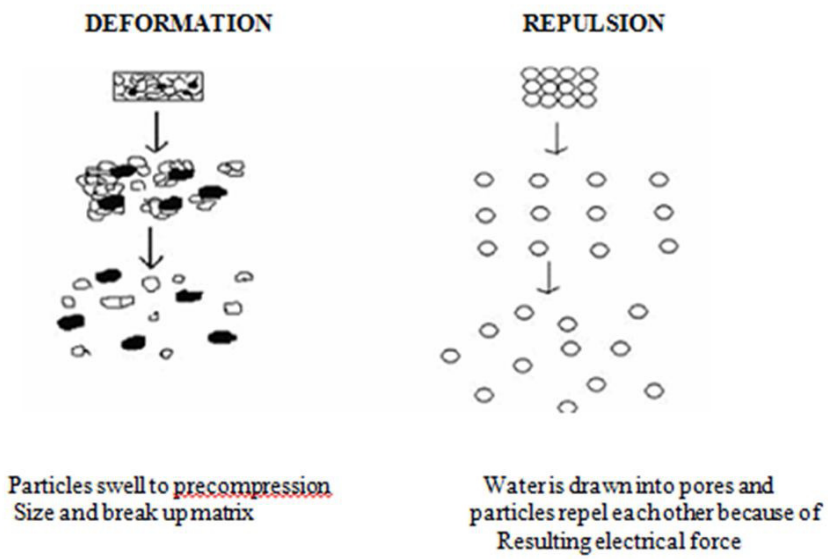


Fig: 4 Disintegration of tablets by deformation and repulsion method.

By enzymatic reaction

Enzymes present in the body also act as disintegrants. These enzymes dearth the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration.

2. REVIEW OF LITERATURE

A. A. Kalanuria *et.al* [23] Migraine is a common and often disabling neurovascular disorder. Changes in the metabolism and the central processing of serotonin, as well as abnormalities in the modulation of the central and peripheral trigeminal nociceptive pathways, have been shown to play significant roles in migraine pathophysiology. Recent evidence suggests that a low serotonin state facilitates activation of the trigeminal nociceptive pathways. In addition, several pharmacological agents that modulate serotonin are used in the treatment of migraine. Specifically there are seven FDA approved, 5-hydroxytryptamine (5-HT) 1B/1D receptor agonists, used for the acute abortive therapy of migraine. Zolmitriptan is one such triptan. Zolmitriptan is available as a tablet, orally disintegrating tablet and as a nasal spray. It is rapidly absorbed and detectable within the plasma, within 2 to 5 minutes for the nasal spray and within 15 minutes for the tablet. Zolmitriptan reaches peak plasma levels in 2–4 hours, with good levels maintained for up to 6 hours. Although the metabolism of zolmitriptan is predominantly hepatic, only 25% of zolmitriptan is bound to plasma proteins. Thus it is unlikely for drug interactions involving the displacement of highly protein-bound drugs. Zolmitriptan is very well tolerated with less than half of participants in clinical trials reporting adverse events, most of which were mild and transient. Although rare, serious cardiovascular events have been reported with all triptans. However, when patients are appropriately selected, zolmitriptan is both, a safe and effective acute migraine abortive agent. In this article, we will first briefly review the biological role of serotonin and the literature linking serotonin to migraine pathophysiology. This will be followed by a comprehensive review of the pharmacodynamics, pharmacokinetics and efficacy of zolmitriptan. Finally, the clinical application of the use of zolmitriptan in migraine therapy will be discussed.

Benjamin *et.al* [24] Migraine headache is a common and potentially debilitating disorder often treated by family physicians. Before diagnosing migraine, serious intracranial pathology must be ruled out. Treating acute migraine is challenging because of substantial rates of nonresponse to medications and difficulty in predicting individual response to a specific agent or dose. Data comparing different drug classes are relatively scarce. Abortive therapy should be used as early as possible after the onset of symptoms. Effective first-line therapies for mild to

moderate migraine are nonprescription nonsteroidal anti-inflammatory drugs and combination analgesics containing acetaminophen, aspirin, and caffeine. Triptans are first-line therapies for moderate to severe migraine, or mild to moderate migraine that has not responded to adequate doses of simple analgesics. Triptans should be avoided in patients with vascular disease, uncontrolled hypertension, or hemiplegic migraine. Intravenous antiemetics, with or without intravenous dihydroergotamine, are effective therapies in an emergency department setting. Dexamethasone may be a useful adjunct to standard therapy in preventing short-term headache recurrence. Intranasal lidocaine may also have a role in relief of acute migraine. Isometheptene-containing compounds and intranasal dihydroergotamine are also reasonable therapeutic options. Medications containing opiates or barbiturates should be avoided for acute migraine. During pregnancy, migraine may be treated with acetaminophen or nonsteroidal anti-inflammatory drugs (prior to third trimester), or opiates in refractory cases. Acetaminophen, ibuprofen, intranasal sumatriptan, and intranasal zolmitriptan seem to be effective in children and adolescents, although data in these age groups are limited.

Vollono C *et.al* [25] Abortive drugs used for migraine in children and adolescents are usually the same as those used in adults. Only a few studies have assessed the efficacy of triptans other than sumatriptan in pediatric migraine. This systematic review describes the evidence concerning the efficacy and tolerability of these triptans. The PubMed research produced 481 results and only seven studies were randomized controlled trials. A total of 11 articles were reviewed. Zolmitriptan and rizatriptan were superior to placebo in most studies. Almotriptan demonstrated a high profile of tolerability. A single study of eletriptan demonstrated no statistical difference between this drug and placebo in terms of both efficacy and tolerability. All studies have reported a good triptan safety profile. The conflicting data regarding triptan efficacy are probably due to differences in populations, methodologies and efficacy measures among the different studies. Triptans are an important option in the symptomatic treatment of childhood and adolescent migraine.

Eiland *et.al* [26] Migraine headaches frequently occur in the pediatric population, with a prevalence of 3% in children 2-7 years of age, 4-11% in children 7-11 years of age, and 8-23% in children 11 years of age and older. Migraine without aura is more than twice as common as

migraine with aura in children. Headaches are the third leading cause of emergency room referrals and rank in the top five health problems of children. The 2004 American Academy of Neurology's treatment parameter for migraine in children and adolescents recommended that nasal sumatriptan be considered for acute treatment; however, data were lacking to make a decision regarding the available oral triptans at that time. The more recently released European guidelines discuss three different triptans for use in children but no specific triptan was recommended. Currently, six of the seven available triptans have been studied for efficacy and safety in the pediatric population; however, only a few well controlled clinical studies have been conducted. Sumatriptan has the most available data on outcomes in general, with nasal sumatriptan showing the most positive results. Nasal sumatriptan is approved in children older than 12 years of age in Europe. Oral sumatriptan does not show any clinical benefit versus placebo in children. Rizatriptan and zolmitriptan have conflicting efficacy and safety data, with most studies favoring the use of oral rizatriptan and nasal zolmitriptan. Almotriptan is the first triptan to obtain a US FDA indication in adolescents with migraines lasting 4 or more hours. This approval was based upon two studies, one large clinical trial and one very small, open-label, pilot study. At this time, there are insufficient data to recommend naratriptan and eletriptan for first- or second-line use in pediatric patients with migraines. There are currently no efficacy data for frovatriptan in pediatric patients, which limits its use in this population. Adverse effects of triptans and pharmacokinetic data in children and adolescents are similar to those in adults. The triptan class should be considered as an acute treatment option for children and adolescents with migraines, although their use is mostly 'off-label'. Of the available triptans, there are more positive efficacy data for sumatriptan and zolmitriptan nasal sprays, and rizatriptan and almotriptan tablets than for the other triptans.

Johnston *et.al* [27] Migraine is a chronic, recurrent, disabling condition that affects millions of people in the US and worldwide. Proper acute care treatment for migraineurs is essential for a full return of function and productivity. Triptans are serotonin (5-HT)(1B/1D) receptor agonists that are generally effective, well tolerated and safe. Seven triptans are available worldwide, although not all are available in every country, with multiple routes of administration, giving doctors and patients a wide choice. Despite the similarities of the available triptans, pharmacological heterogeneity offers slightly different efficacy profiles. All triptans are

superior to placebo in clinical trials, and some, such as rizatriptan 10 mg, eletriptan 40 mg, almotriptan 12.5 mg, and zolmitriptan 2.5 and 5 mg are very similar to each other and to the prototype triptan, sumatriptan 100 mg. These five are known as the fast-acting triptans. Increased dosing can offer increased efficacy but may confer a higher risk of adverse events, which are usually mild to moderate and transient in nature. This paper critically reviews efficacy, safety and tolerability for the different formulations of sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, eletriptan and frovatriptan.

Francis *et.al* [28] Cluster headache (CH) is a rare and disabling primary headache disorder. CH attacks are unilateral, short, severe headaches associated with ipsilateral autonomic symptoms that occur in a periodic fashion. We provide a systematic review and meta-analysis of existing trials of pharmacotherapy for CH and evidence-based suggestions for acute abortive treatment and preventive therapy for cluster headache. Prospective, double-blind, randomized controlled trials of any pharmacologic agent for the symptomatic relief or prevention of CH were included in this evidence-based review. The main outcomes considered were headache response and pain-free response at 15 and 30 minutes for acute treatment trials, and the cessation of CH attacks within a specific time period or the number of days on which CH attacks occurred for preventive trials. Twenty-seven trials were included in the analysis. The American Academy of Neurology quality criteria were used to assess trial quality and to grade advisements. Based on the evidence, for acute treatment of CH, Level A advice can be given for subcutaneous sumatriptan 6 mg, zolmitriptan nasal spray 5 mg and 10 mg, and 100% oxygen 6-12 L/min. Level B advice can be given for sumatriptan nasal spray 20 mg and oral zolmitriptan 5 mg and 10 mg. For the prevention of CH, Level B advice can be given for intranasal civamide 100 microg daily and suboccipital steroid injections, and Level C advice can be given for verapamil 360 mg, lithium 900 mg, and melatonin 10 mg.

Majumdar *et.al* [29] Cluster headache is a primary headache disorder with the distinct clinical features: unilaterality, extreme pain, cranial autonomic features and periodicity. The prevalence of the disorder is 0.1% in adults and with a male predominance. The age of onset is usually in the second and third decade of life but the onset in the first decade is recognised. We describe our experience of cluster headache in children and review the literature. We have

attempted to define the clinical features of cluster headache in children as compared to adults, the role of clinical investigations, reliability of clinical diagnosis, effective treatment and management.

Fotuhi *et.al* [30] Vestibular migraine (VM), also known as migraine-associated vertigo, is a common cause of dizziness in adults. We performed a comprehensive literature search regarding treatment for VM or migraine-associated vertigo during the period of 1990-2008 and used, individually or in combination, the search terms VM, migraine-associated vertigo, migraine-associated dizziness, migrainous vertigo, migraine and vertigo, migraine and disequilibrium, and headache and vertigo. We found nine publications that address treatment strategies for VM. One small randomized clinical trial found some benefit from the use of zolmitriptan for abortive treatment of VM. The other eight observational studies showed marginal improvement with migraine prophylactic medications such as nortriptyline, verapamil, or metoprolol. Until more specific treatment options become available, patients with VM need to be managed with similar prophylactic and abortive strategies as those used for migraine in adults.

Tyagi *et.al* [31] Cluster headache (CH) is a strictly unilateral headache that occurs in association with cranial autonomic features. It is an excruciating syndrome and is probably one of the most painful conditions known to exist, with some female patients describing each attack as being worse than childbirth. CH responds to specific therapies, thereby underlying the importance of distinguishing it from other primary headache syndromes and initiating appropriate treatments. This article reviews the evidence base for the medical treatments used in ICH.

Silver, Shawna *et.al* [32] To undertake a meta-analysis of all randomised controlled trials (RCTs) on the acute pharmacologic treatment of children and adolescents with migraine headache.the methods used totally, 139 abstracts of clinical trials specific to the acute treatment of paediatric migraine were appraised. Inclusion criteria required clinical trials to be randomised, blinded, placebo-controlled studies with comparable endpoints. Non- English language

publications were excluded. 11 clinical trials qualified for inclusion in the final meta-analysis. Two endpoints were analysed: the proportion of patients with (1) headache relief, and (2) complete pain relief, 2 h post-treatment. And the conclusion Despite the pharmacological options for the management of acute migraine, few RCTs in the paediatric population exist. Composite data demonstrate that only ibuprofen and sumatriptan are significantly more effective than placebo in the generation of headache relief in children and adolescents.

Peterlin, B Lee *et.al* [33] Migraine is a common, often disabling, neurovascular disease that has been shown to be associated with abnormal serotonergic activity. Drugs that modulate serotonin receptors are commonly used in the acute treatment of a migraine attack. Zolmitriptan, a 5-hydroxytryptophan(1B/1D) receptor agonist, is once such drug that is used in acute migraine therapy. Zolmitriptan is FDA approved for the treatment of acute migraine attacks and there is recent literature demonstrating its efficacy in the acute treatment of cluster attacks. It is rapidly absorbed and is detectable in the plasma within 2 - 5 min for the nasal spray formulation and within 15 min for the oral formulations. Zolmitriptan reaches peak plasma levels in 2 - 4 h and significant plasma levels are maintained for up to 6 h and lower levels for over 15 h. As zolmitriptan's metabolism is predominantly hepatic, patients with severe hepatic impairment should not receive zolmitriptan. However, only 25% of zolmitriptan is bound to plasma proteins and thus it is unlikely for drug interactions involving the displacement of highly protein-bound drugs. Zolmitriptan is generally very well tolerated and less than half of patients in clinical trials have reported adverse events, most of which are mild and transient, although rare serious cardiovascular events have been reported with all triptans. When patients are appropriately selected, zolmitriptan is both a safe and effective acute care migraine treatment. In this review the biological role of serotonin and its receptors is covered, followed by an in-depth review of the pharmacodynamics, pharmacokinetics and efficacy of zolmitriptan. Finally, the clinical application of zolmitriptan's use in patients is dicussed.

Sternieri *et.al* [34] Recent progress in the treatment of primary headaches has made available specific, effective and safe medications for these disorders, which are widely spread among the general population. One of the negative consequences of this undoubtedly positive progress is the risk of drug-drug interactions. This review is the first in a two-part series on

pharmacokinetic drug-drug interactions of headache medications. Part I addresses acute treatments. Part II focuses on prophylactic treatments. The overall aim of this series is to increase the awareness of physicians, either primary care providers or specialists, regarding this topic. Pharmacokinetic drug-drug interactions of major severity involving acute medications are a minority among those reported in literature. The main drug combinations to avoid are: i) NSAIDs plus drugs with a narrow therapeutic range (i.e., digoxin, methotrexate, etc.); ii) sumatriptan, rizatriptan or zolmitriptan plus monoamine oxidase inhibitors; iii) substrates and inhibitors of CYP2D6 (i.e., chlorpromazine, metoclopramide, etc.) and -3A4 (i.e., ergot derivatives, eletriptan, etc.), as well as other substrates or inhibitors of the same CYP isoenzymes. The risk of having clinically significant pharmacokinetic drug-drug interactions seems to be limited in patients with low frequency headaches, but could be higher in chronic headache sufferers with medication overuse.

Dowson *et.al* [35] As part of an optimal strategy for the management of migraine, the individual needs and preferences of patients need to be considered when of patients need to be considered when prescribing treatments. Zolmitriptan has been available as a conventional oral tablet for more than seven years, and is established as a highly effective, well-tolerated compound for the acute treatment of migraine. A bioequivalent, orally disintegrating tablet (ODT) of zolmitriptan, which dissolves on the tongue without the need for additional fluid intake, has been developed. In a study designed to compare patient preference for zolmitriptan ODT and conventional oral sumatriptan tablets, > 60% of the 186 patients questioned had an overall preference for zolmitriptan ODT, with > 80% of patients reporting that this was the more convenient and less disruptive therapy to take. Approximately 90% of patients agreed that, unlike a conventional tablet, zolmitriptan ODT can be taken wherever and whenever a migraine occurs. When patient preference for zolmitriptan ODT and the ODT formulation of rizatriptan was compared in 171 migraineurs, 70% had an overall preference for zolmitriptan ODT to be superior to rizatriptan ODT with respect to taste and aftertaste, as well as packaging. In summary, not only is zolmitriptan ODT a convenient tablets, such as the sumatriptan oral tablet, but patients generally consider it to be a more attractive option for the acute treatment of migraine than the orally disintegrating version of rizatriptan.

Tepper *et.al* [36] The triptans are 5-HT(1B/1D) agonists used as migraine and cluster-specific agents. Seven are in commercial use worldwide; in order of release these are sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, frovatriptan and eletriptan. Sumatriptan has been in clinical use since 1991, and although postmarketing studies have stimulated much debate of triptan strengths and weaknesses, their overall safety profile appears excellent. The most serious adverse events are cardiovascular, due to coronary artery narrowing as a consequence of coronary artery 5-HT(1B) receptor activity. Triptans are contraindicated in patients with vascular disease. Other events are even more rare, and include the potential for drug-drug interactions, based on metabolic elimination pathways. Serotonin syndrome has been a concern, but one large prospective study failed to document a single case, and reports are sporadic and not clearly causative.

Villalón *et.al* [37] Migraine treatment has evolved into the scientific arena, but it seems still controversial whether migraine is primarily a vascular or a neurological dysfunction. Irrespective of this controversy, the levels of serotonin (5-hydroxytryptamine; 5-HT), a vasoconstrictor and a central neurotransmitter, seem to decrease during migraine (with associated carotid vasodilatation) whereas an i.v. infusion of 5-HT can abort migraine. In fact, 5-HT as well as ergotamine, dihydroergotamine and other antimigraine agents invariably produce vasoconstriction in the external carotid circulation. The last decade has witnessed the advent of sumatriptan and second generation triptans (e.g. zolmitriptan, rizatriptan, naratriptan), which belong to a new class of drugs, the 5-HT1B/1D/1F receptor agonists. Compared to sumatriptan, the second-generation triptans have a higher oral bioavailability and longer plasma half-life. In line with the vascular and neurogenic theories of migraine, all triptans produce selective carotid vasoconstriction (via 5-HT1B receptors) and presynaptic inhibition of the trigeminovascular inflammatory responses implicated in migraine (via 5-HT1D/5-ht1F receptors). Moreover, selective agonists at 5-HT1D (PNU-142633) and 5-ht1F (LY344864) receptors inhibit the trigeminovascular system without producing vasoconstriction. Nevertheless, PNU-142633 proved to be ineffective in the acute treatment of migraine, whilst LY344864 did show some efficacy when used in doses which interact with 5-HT1B receptors. Finally, although the triptans are effective antimigraine agents producing selective cranial vasoconstriction, efforts are being made to develop other effective antimigraine alternatives acting via the direct blockade of

vasodilator mechanisms (e.g. antagonists at CGRP receptors, antagonists at 5-HT7 receptors, inhibitors of nitric oxide biosynthesis, etc). These alternatives will hopefully lead to fewer side effects.

Dowson *et.al* [38] Preclinical studies have shown that zolmitriptan is a selective serotonin 5-HT(1B/1D) receptor agonist (triptan). Randomised, placebo-controlled, double-blind trials in patients with migraine have shown that zolmitriptan has good efficacy measured using 2 h response and pain-free rates. Migraine-associated symptoms, including nausea, photophobia and phonophobia, are also improved with zolmitriptan. Oral zolmitriptan (2.5 and 5 mg) has an onset of action within 45 min and efficacy is sustained in most patients who respond at 2 h. The orally-disintegrating zolmitriptan tablet has the advantage that it may be taken immediately, without the need for additional fluids, any time a migraine headache occurs. Patients may benefit in terms of improved efficacy from the convenience of the disintegrating tablet, since there is evidence that taking triptan therapy as early as possible in an attack is advantageous. For similar reasons, as well as improved efficacy, a nasal spray formulation is in development. Zolmitriptan is effective in the treatment of migraine associated with menses and migraine with aura. There is no tachyphylaxis following repeated doses for multiple attacks of migraine over a prolonged period of time. Compared to placebo, the incidence of persistent migraine headache is reduced by zolmitriptan and recurrent migraine headache occurs less frequently. Zolmitriptan has also shown efficacy in the treatment of persistent and/or recurrent migraine headache. Comparative clinical studies have shown overall that zolmitriptan has similar or superior efficacy to sumatriptan in the treatment of migraine. Specifically, zolmitriptan 2.5 mg was significantly more effective than sumatriptan 25 or 50 mg according to a number of end points, including headache response at 2 h. Oral zolmitriptan is also effective in the acute treatment of cluster headache. Zolmitriptan is generally well tolerated, with most adverse events being mild-to-moderate, transient and resolving without intervention or the need for treatment withdrawal. The consistent efficacy in treating all types of migraine and the choice of available formulations make zolmitriptan acceptable to patients and a suitable first-line therapy for the treatment of migraine.

Adelman *et.al* [39] Triptans, beginning with sumatriptan, have revolutionized the treatment of migraine. New triptans in several formulations will soon become available in the United States. Although the similarities of these 5-hydroxytryptamine (5-HT) 1B/1D receptor agonists outweigh their differences, important differences in pharmacokinetics and clinical responses do exist. Subcutaneous sumatriptan has the most rapid onset of action and greatest efficacy but the most adverse effects. Intranasal sumatriptan also has rapid onset of action, but at 2 hours its efficacy is comparable to that of oral zolmitriptan. Of the oral triptans, rizatriptan seems to have the greatest early efficacy. Both rizatriptan and zolmitriptan are now available as rapidly dissolving wafers. Almotriptan, the newest of the triptans, has a response rate similar to that of oral sumatriptan and may produce fewer adverse effects. Naratriptan and frovatriptan, with their slow onset, high tolerability, and long half-lives, may have a role in aborting prolonged migraine attacks and in headache prevention. Eletriptan at higher doses (80 mg) has a response rate approaching that of rizatriptan but may be limited by potential side effects. The many triptans available offer the opportunity to individualize migraine treatment, depending on the patient's attack characteristics, tolerance, and preferences.

Tfelt-Hansen *et.al* [40] Triptans are a new class of compounds developed for the treatment of migraine attacks. The first of the class, sumatriptan, and the newer triptans (zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan and frovatriptan) display high agonist activity at mainly the serotonin 5-HT1B and 5-HT1D receptor subtypes. As expected for a class of compounds developed for affinity at a specific receptor, there are minor pharmacodynamic differences between the triptans. Sumatriptan has a low oral bioavailability (14%) and all the newer triptans have an improved oral bioavailability and for one, risatriptan, the rate of absorption is faster. The half-lives of naratriptan, eletriptan and, in particular, frovatriptan (26 to 30h) are longer than that of sumatriptan (2h). These pharmacokinetic improvements of the newer triptans so far seem to have only resulted in minor differences in their efficacy in migraine. Double-blind, randomised clinical trials (RCTs) comparing the different triptans and triptans with other medication should ideally be the basis for judging their place in migraine therapy. In only 15 of the 83 reported RCTs were 2 triptans compared, and in 11 trials triptans were compared with other drugs. Therefore, in all placebo-controlled randomised clinical trials, the relative efficacy of the triptans was also judged by calculating the therapeutic gain (i.e. percentage response for active minus percentage response for placebo). The

mean therapeutic gain with subcutaneous sumatriptan 6mg (51%) was more than that for all other dosage forms of triptans (oral sumatriptan 100mg 32%; oral sumatriptan 50mg 29%: intranasal sumatriptan 20mg 30%; rectal sumatriptan 25mg 31%; oral zolmitriptan 2.5mg 32%; oral rizatriptan 10mg 37%; oral eletriptan 40mg 37%; oral almotriptan 12.5mg 26%). Compared with oral sumatriptan 100mg (32%), the mean therapeutic gain was higher with oral eletriptan 80mg (42%) but lower with oral naratriptan 2.5mg (22%) or oral frovatriptan 2.5mg (16%). The few direct comparative randomised clinical trials with oral triptans reveal the same picture. Recurrence of headache within 24 hours after an initial successful response occurs in 30 to 40% of sumatriptan-treated patients. Apart from naratriptan, which has a tendency towards less recurrence, there appears to be no consistent difference in recurrence rates between the newer triptans and sumatriptan. Rizatriptan with its shorter time to maximum concentration (tmax) tended to produce a quicker onset of headache relief than sumatriptan and zolmitriptan. The place of triptans compared with non-triptan drugs in migraine therapy remains to be established and further RCTs are required.

Egilius L H Spierings *et.al* [41] Migraine is a common, often disabling, neurovascular disease that has been shown to be associated with abnormal serotonergic activity. Drugs that modulate serotonin receptors are commonly used in the acute treatment of a migraine attack. Zolmitriptan, a 5-hydroxytryptophan$_{1B/1D}$ receptor agonist, is once such drug that is used in acute migraine therapy. Zolmitriptan is FDA approved for the treatment of acute migraine attacks and there is recent literature demonstrating its efficacy in the acute treatment of cluster attacks. It is rapidly absorbed and is detectable in the plasma within 2 – 5 min for the nasal spray formulation and within 15 min for the oral formulations. Zolmitriptan reaches peak plasma levels in 2 – 4 h and significant plasma levels are maintained for up to 6 h and lower levels for over 15 h. As zolmitriptan's metabolism is predominantly hepatic, patients with severe hepatic impairment should not receive zolmitriptan. However, only 25% of zolmitriptan is bound to plasma proteins and thus it is unlikely for drug interactions involving the displacement of highly protein-bound drugs. Zolmitriptan is generally very well tolerated and less than half of patients in clinical trials have reported adverse events, most of which are mild and transient, although rare serious cardiovascular events have been reported with all triptans. When patients are appropriately selected, zolmitriptan is both a safe and effective acute care migraine treatment. In this review the biological role of serotonin and its receptors is covered, followed by an in-depth review of

the pharmacodynamics, pharmacokinetics and efficacy of zolmitriptan. Finally, the clinical application of zolmitriptan's use in patients is dicussed.

Ch. Anil kumar *et.al* [42]) Zolmitriptan is a Selective Serotonin receptor agonist of the 1B and 1D subtype. Used in the acute treatment of Migraine attacks with or without aura and headaches. The present research work is aimed at developing a Formulate and Evaluated of an Oro dispersible tablet dosage form of Zolmitriptan. The target of these new oral dissolving/disintegrating dosage forms have generally been pediatric, geriatric, bedridden and developmentally disabled patients and also patients with persistent nausea, who are in traveling, or who have little or no access to water are also good candidates for ODTs Direct Compression method was employed for blending of drug with polymers in the given ratio as a 9 formulations. The prepared powder blends were then compressed into tablets using the necessary Superdisintegrants (CCS, CP, and SSG) and Excipients. The tablets were evaluated for Weight variation, thickness,hardness, friability, Drug Content and Disintegrating Time (Sec) were subjected to a 10 minutes in vitro drug release studies (USP dissolution rate test apparatus II, 50 rpm, 370C ±0.50C) using phosphate buffer, pH 6.8 as a dissolution medium (900ml). The amount of Zolmitriptan released from the tablet formulations at different time intervals was estimated using a UV spectroscopy method. The formulations that showed a considerable retardation of the drug release are considered promising.

Andrew J. Dowson *et.al* [43] A simple,selective,linear,presice and accurate RP-HPLC method was developed and validated for rapid assy of zolmitriptan in tablet dosage form.Isocratic solution at a flow rate of 1.0ml/min was eemployed on symmetry C18(280*4.6mm,5µm in paticle size) at ambient temperature.the mobile phase consisted of 0.01%triethyl amine :acetonitrile:0.02M $NH_4H_2PO_4$;28.2:25:46.8(V/V/V).The uv detection wavelength was 225nm and 20µl sample was injected,the retention time for zolmitriptan was 3.705 min.the percentage RSD for precision and accuracy of themethod was found to be less than 2%.the method was validated as per ich guide lines.the method was successfully applied for routine analysis of zolmitriptan in tablet dosage form.

Diener HC *et.al* [44] A simple sensitive and specific reverse phase high performance liquid chromatographic method has been developed for the determination of zolmitriptan tablet dosage forms.chromatographic separation was achieved on a kromasil C18(150*4.6mm),5.0µm column with a 750ml of 0.01 anhydrous dipotassium hydrogen orthophosphate, added 250ml of methanol and fixed as a mobile phase ,detection was at 230nm.response was a linear function of sconcentration in the range 2-0.01µg/ml for Zolmitriptan, LOD and LOQ for Zolmitriptan was found to be 0.01µg/ml and 0.03µg/ml.

Accuracy (recoveries 90-97%) and reproducibility were found to satisfactory

3. AIM AND OBJECTIVE

AIM

The aim of the present study was to formulate Zolmitriptan oral disintegrating tablets by direct compression method and to evaluate the formulations for various parameters to produce oral dosage form with better pharmaceutical and therapeutic properties.

OBJECTIVE

The objective of the present investigation was to prepare Oral disintegrating tablets's of Zolmitriptan and to evaluate the effect of different superdisintegrants on their disintegration time and In vitro dissolution characteristics with increased bioavailability, rapid absorption, effective therapy and patient compliance because fast onset of action is desirable in epilepsy without the use of water.

Based on the evaluation parameters, the formulation with better disintegration and dissolution profile when compared to the other formulations.

4. PLAN OF WORK

The study was proposed to carry out in the following:

A.1.Formulaion ad evaluation of Oral Disintegrantion tablets of Zolmitriptan by using Superdisintegrants (Crosscarmellose Sodium, Sodium Starch Glycolate and Crosspovidone) in different concentrations by using direct compression method.

B. Pre compression studies:

1 .FTIR

2. Angle of repose

3. Bulk density

4. Tapped density

5. Compressibility index

C. Formulation of tablets

D. **Post compression studies**:

1. Tablet thickness

2. Weight variation

3. Hardness

4. Friability

5 .Disintegration test

6. Dissolution test.

7**.** Drug content estimation

E. kinetic release studies

5. PROFILES

ZOLMITRIPTAN [45]

Drug Name : Zolmitriptan

Category : Serotonin receptor agonist used in the acute treatment of migraine attacks

Empirical formulae : C16H21N3O2

Molecular weight : 287.36

Solubility : it is soluble in water and methanol and HCL

Pharmacokinetic data:-

Bioavailability : 40% oral

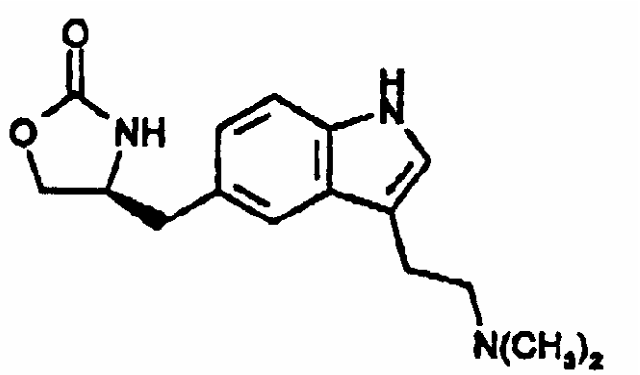
Protien binding : 25%

Metabolism : Hepatic (CYP1A2-mediated, to active metabolite)

Half life : 3 hours

Excretion : Renal (65%) and fecal (35%)

Chemical structure :



Chemical name:

(*S*)-4-({3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl}methyl)-1,3-oxazolidin-2-one

Mechanism of action

Zolmitriptan binds with high affinity to human recombinant 5-HT1D and 5-HT1B receptors. It exhibits modest affinity for 5-HT1A receptors, but has no significant affinity (as measured by radio ligand binding assays) or pharmacological activity at 5-HT2 , 5-HT3 , 5-HT4 , alpha1- , alpha2- , or beta1- adrenergic; H1 , H2 , histaminic; muscarinic; dopamine1 , or dopamine 2 receptors. The N-desmethyl metabolite also has high affinity for 5-HT1B/1D and modest affinity for 5-HT1A receptors. Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (vasoactive intestinal peptide, substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of zolmitriptan for the treatment of migraine headache can most likely be attributed to the agonist effects at the 5-HT $_{1B/1D}$ receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

CLINICAL PHARMACOKINETIC AND BIOAVAILABILITY

Absorption

Zolmitriptan is well absorbed after oral administration for both the conventional tablets and the orally disintegrating tablets. Zolmitriptan displays linear kinetics over the dose range of 2.5 to 50 mg. The AUC and C of zolmitriptan are similar following administration of ZOMIG Tablets and ZOMIGZMT Orally Disintegrating Tablets, but the T is somewhat later with ZOMIG-ZMT, with a median T of 3 hours for the orally disintegrating tablet compared with 1.5 hours for the conventional tablet. The AUC, Cmax , and Tmax for the active N-desmethyl metabolite are similar for the two formulations. During a moderate to severe migraine attack, mean AUC and C for zolmitriptan, dosed as a conventional tablet, were decreased by 40% and 25%, respectively, and mean T was delayed by one half hour compared to the same patients during a migraine free period. Food has no significant effect on the bioavailability of zolmitriptan. No accumulation occurred on multiple dosing.

Distribution

Mean absolute bioavailability is approximately 40-50%. The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of zolmitriptan is 25% over the concentration range of 10- 1000ng/mL.

Metabolism

Zolmitriptan is converted to an active N-desmethyl metabolite such that the metabolite concentrations are about two-thirds that of zolmitriptan. Because the 5HT potency of the metabolite is 2 to 6 times that of the parent, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration.

Elimination

Total radioactivity recovered in urine and feces was 65% and 30% of the administered dose, respectively. About 8% of the dose was recovered in the urine as unchanged zolmitriptan. Indole acetic acid metabolite accounted for 31% of the dose, followed by N-oxide (7%) and N-desmethyl (4%) metabolites. The indole acetic acid and N-oxide metabolites are inactive. Mean total plasma clearance is 31.5mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

POLYMER PROFILE

CROSCARMELLOSE SODIUM [46]

Nonproprietary Name:

BP	:	Croscarmellose Sodium
JP	:	Croscarmellose Sodium
PhEur	:	Croscarmellose Sodium
USP-NF	:	CroscarmelloseSodium

Synonym

Ac-Di-Sol; Carmellosum Natricum Conexum, Crosslinked Carboxy methyl cellulose Sodium, Explocel, Modified cellulose gum, Nymcel ZSX, Pharmacel XL, Primellose, Solutab,Vivasol.

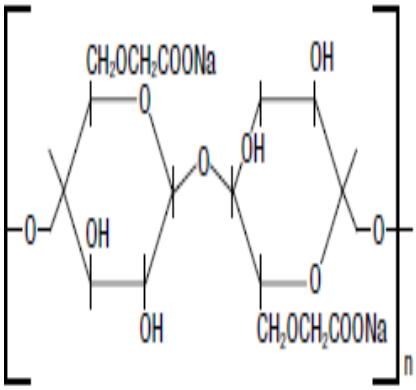
Chemical name

Cellulose, carboxymethyl ether, sodium salt, cross linked.

Empirical formula **:** C8H16O8

Molecular weight **:** 240.20784

Structural formula **:**



Functional category **:** Tablet and capsule disintegrant.

Applications in pharmaceutical formulation and technology

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules , tablets, and granules. In tablet formulations, Croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the Croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.(Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Description

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Density (true) **:** 1.543 g/cm3 for Ac-Di-Sol

Solubility

Insoluble in water, although Croscarmellose sodium rapidly swells to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Incompatibilities

The efficacy of disintegrants, such as Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury, and zinc.

Stability and storage conditions

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 308C for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

SODIUM STARCH GLYCOLATE [46]

Nonproprietary Name

BP : Sodium Starch Glycolate

PhEur : Sodium Starch Glycolate

USP-NF : Sodium Starch Glycolate

Synonyms

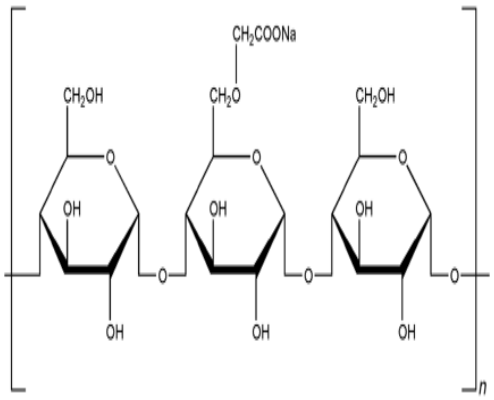
Carboxymethyl starch, sodium salt carboxymethylamylum natricum, Explosol, Explotab, Glycolys,Primojel, starch carboxymethyl ether, sodium salt,Tablo; Vivastar P.

Chemical name **:** Sodium carboxymethyl starch.

Empirical formula **:** C24H44O6Na

Molecular weight **:** 222.25.

Structural formula



Functional category **:** Tablet and capsule disintegrant.

Applications in pharmaceutical formulation and technology

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.
- It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling. Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description

Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of: granules, irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded, 10–35 mm in size; compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water.

Density(true) **:** 1.56 g/cm3 for Primojel;
1.49 g/cm3 for Tablo.

Melting point **:** Does not melt, but chars at approximately 200C.

Solubility **:** Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Incompatibilities **:** Sodium starch glycolate is incompatible with ascorbic acid.

Stability and storage conditions

Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

CROSSPOVIDONE [46]

Nonproprietary Names:

BP **:** Crospovidone
PhEur **:** Crospovidone
USP-NF **:** Crospovidone

Synonyms

Crospovidonum, Crospopharm, crosslinked povidone;, E1202, Kollidon CL; Kollidon CL-M, Polyplasdone XL, Polyplasdone XL-10, polyvinylpolypyrrolidon,; PVPP, 1-vinyl-2-pyrrolidinone homopolymer.

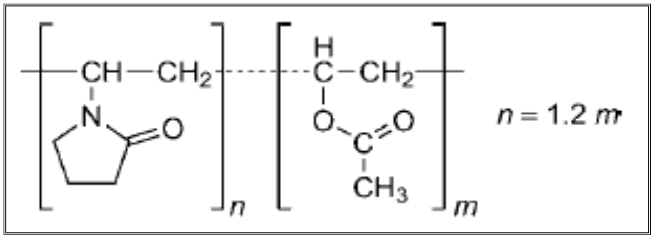
Chemical Name **:** 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical formula **:** (C6H9No)n

Molecular weight **:** >1 000 000

The usp32–nf27 describes crospovidone as a water-insoluble synthetic crosslinked shomopolymer of n-vinyl-2-pyrrolidinone. An exact determination of the molecular weight has not been established because of the insolubility of the material.

Structural formula



Functional category : Tablet disintegrant.

Applications in pharmaceutical formulations and technology

- Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles.
- Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation.
- crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Description

Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Density : 1.22 g/cm^3

Incompatabilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Stability and storage conditions:

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

EXCEPIENT PROFILE

SUCRALOSE [47]

Nonproprietary Name **:** USP-NF: Sucralose

Synonyms:

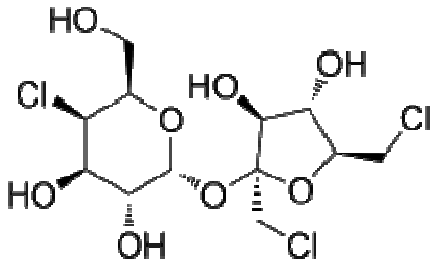
Splenda; sucralosa; sucralosum; SucraPlus; TGS; 10,40,60-trichlorogalactosucrose; 4,10,60 Trichloro-4,10,60-trideoxy-galacto-sucrose.

Chemical Name **:** 1,6-Dichloro-1,6-dideoxy-b-D-fructofuranosyl-4-chloro-4-deoxya- D-galactopyranoside

Empirical formula : $C_{12}H_{19}C_{13}O_8$

Molecular weight : 397.64

Structural formula



Functional category : Sweetening agent.

Applications in pharmaceutical formulation and technology

Sucralose is used as a sweetening agent in beverages, foods, and pharmaceutical applications. It has a sweetening power approximately 300–1000 times that of sucrose and has no aftertaste. It has no nutritional value, is noncariogenic, does not promote dental caries, and produces no glycemic response.

Description

Sucralose is a white to off-white colored, free-flowing, crystalline powder.

Density (true) : 1.63 g/cm3

Melting point : 1308C (for anhydrous crystalline form); 36.58C (for pentahydrate).

Stability and Storage Conditions:

Sucralose is a relatively stable material. In aqueous solution, at highly acidic conditions (pH < 3), and at high temperatures (4358C), it is hydrolyzed to a limited extent, producing 4-chloro-4- deoxygalactose and 1,6-dichloro-1,6-dideoxyfructose. In food products, sucralose remains stable throughout extended storage periods, even at low pH. However, it is most stable at pH 5–6. Sucralose should be stored in a well-closed container in a cool, dry place, at a temperature not exceeding 218C. Sucralose, when heated at elevated temperatures, may break down with the release of carbon dioxide, carbon monoxide, and minor amounts of hydrogen chloride.

MAGNESIUM STEARATE [47]

Nonproprietary names:

BP	**:** Magnesium Stearate
JP	**:** Magnesium Stearate
PhEur	**:** Magnesium Stearate
USP-NF	**:** Magnesium Stearate

Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesiistearas; magnesium octadecanoate; octadecanoic acid, magnesiumsalt; stearic acid, magnesium salt; Synpro 90.

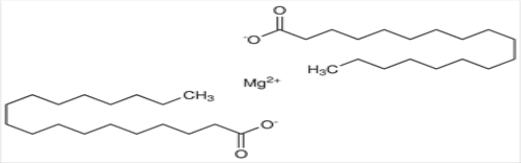
Chemical Name **:** Octadecanoic acid magnesium salt

Emperical formula **:** $C_{36}H_{70}MgO_4$

Molecular weight **:** 591.24

The USP32–NF27 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{32}H_{62}MgO_4$). The PhEur 6.5 describes magnesium stearate as a mixture of solid organic acids consisting mainly of variable proportions of magnesium stearate and magnesium palmitate obtained from sources of vegetable or animal.

Structural formula



Functional category : Tablet and capsule lubricant

Applications in pharmaceutical formulation and technology

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant incapsule and tablet manufacture at concentrations between 0.25%and 5.0% w/w. It is also used in barrier creams.

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Density (true) **:** 1.092 g/cm^3

Melting range **:** 117–1508C

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Incompatabilities

Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

Safety

Magnesium stearate is widely used as a pharmaceutical excipients and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation. No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worst case daily intake and heavy metal composition. Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled. Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice

Stability and storage conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

MANNITOL [46]

Nonproprietary names

BP : Mannitol

JP : D-Mannitol

PhEur : Mannitol

USP : Mannitol

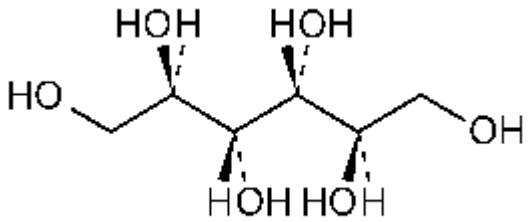
Synonyms : Cordycepic acid, C*PharmMannidex, E421, Emprove,manna sugar; D-mannite; mannite, mannitolum, Mannogem, Pearlitol.

Chemical formula : D-Mannitol.

Empirical formula : $C_6H_{14}O_6$

Molecular weight : 182.17

Chemical structure



Functional category

Diluent; plasticizer, sweetening agent, tablet and capsule diluents, therapeutic agent, tonicity agent

Applications in pharmaceutical formulation and technology:

- Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.
- Mannitol may be used in direct-compression tablet applications, For which the granular and spray-dried forms are available,or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth Feel'. In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use.
- Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations,and as a carrier in dry powder inhalers.It is also used as a diluent in rapidly dispersing oral dosage forms.
- It is used in food applications as a bulking agent. Therapeutically, mannitol administered parenterally is used as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure. Given orally, mannitol is not absorbed significantly from the gastrointestinal tract, but in large doses it can cause osmotic diarrhea.

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or freeflowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts

a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Density (true) : 1.514 g/cm^3

Incompatabilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.(19) Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation. Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.

Stability and storage conditions:

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Millard reactions. The bulk material should be stored in a well-closed container in a cool, dry place.

COLLOIDAL SILICON DIOXIDE [46]

Nonproprietary names:

BP	: Colloidal Anhydrous Silica
JP	: Light Anhydrous Silicic Acid
PhEur	: Silica, Colloidal Anhydrous
USP-NF	: Colloidal Silicon Dioxide

Synonyms

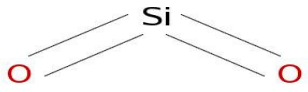
Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; colloidal silica; fumed silica fumed silicon dioxide; hochdisperses silicum dioxide, SAS,silica colloidalis anhydrica; silica sol; silicic anhydride, Silicon dioxide colloidal, silicon dioxide fumed, synthetic amorphous silica, Wacker HDK.

Chemical name : Silica

Empirical formula **:** SiO_2

Molecular weight **:** 60.08

Structural formula:



Functional category

Adsorbent, anti caking agent, Emulsion stabilizer, glident, suspending agent,tablet disintegrant, Thermal stabilizer, viscosity-increasing agent.

Applications in pharmaceutical formulation and technology

- Colloidal silicon dioxide is widely used in pharmaceuticals,Cosmetics and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.
- Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. Colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles.
- Colloidal silicon dioxide is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.
- Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate.
- Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres,as a thickening agent for topical preparations,and has been used to aid the freeze-drying of nanocapsules and nanosphere suspensions.

Description

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored,odorless, tasteless, amorphous powder.

Density(bulk) **:** 0.029–0.042 g/cm3

Melting point **:** 16008C

Solubility

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 258C (pH 7).

Specific gravity **:** 2.2

Incompatabilities **:** Incompatible with diethylstilbestrol preparations.

Safety

Colloidal silicon dioxide is widely used in oral and topical pharmaceutical products and is generally regarded as an essentially nontoxic and nonirritant excipient. However, intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas. Colloidal silicon dioxide should therefore not be administered parenterally.

Stability and storage conditions

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates.Colloidal silicon dioxide powder should be stored in a well-closed container.

CITRIC ACID [48]:

Excipient Name **:** citric acid

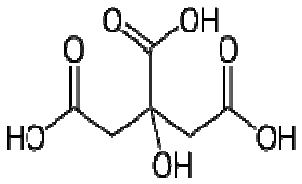
Category

Citric acid is a weak organic acid with the formula C6H8O7. It is a natural preservative/conservative and is also used to add an acidic or sour taste to foods and drinks.

Molecular weight **:** 192.12352

Emperical formula **:** C6H8O7

Chemical structure **: Citric acid**



IUPAC Name **:** 2-hydroxypropane-1,2,3-tricarboxylic acid

Solubility **:** Very soluble in ethanol[49]
Soluble in ether, ethyl acetate, insoluble in benzene, chloroform

Anti coagulants **:** Agents that prevent clotting.

Chelating agents

Chemicals that bind to and remove ions from solutions. Many chelating agents function through the formation of coordination complexes with metals.

Description : citric acid is a white crystalline powder.

Odour : Odorless

BIO MEDICAL EFFECTS AND TOXICITY:

Absorption, distribution, and metabolism

A portion of the circulating (mainly metabolic but also ingested) citric acid is excreted in urine, with 24-hour urine reference values between 1.5 and 3.68 mmol, corresponding to 0.29-0.71 g citric acid excreted per person per day.

Metabolism/ matebolites

Citric acid is a normal metabolite and an intermediate in cellular oxidative metabolism ... The acid is formed in the mitochondrion after condensation of acetate with oxaloacetate. The six-carbon acid is then successively degraded to a series of four-carbon acids, effectively accomplishing oxidation of acetate in the cell.

In human (as well as in animal and plant) physiology, citric acid is a very common intermediate in one of the central biochemical cycles, the Krebs or tricarboxylic acid cycle, which takes place in every cell. It completes the breakdown of pyruvate formed from glucose through glycolysis, thereby liberating carbon dioxide and a further four hydrogen atoms which are picked up by electron transport molecules. Thus, in man approximately 2 kg of citric acid are formed and metabolised every day. This physiological pathway is very well developed and capable of processing very high amounts of citric acid as long as it occurs in low concentrations.

Citric acid in reaction with enzyme citratase /citrate lyase/ yields oxaloacetic acid & acetic acid.

Cosmetics and pharmaceutical applications

- Citric acid is widely used as a pH adjusting agent in creams and gels of all kinds. In this role, it is classified in most jurisdictions as a processing aid and so does not need to be listed on ingredient lists.
- Citric acid is an alpha hydroxy acid and used as an active ingredient in chemical peels.
- Citric acid is commonly used as a buffer to increase the solubility of brown heroin. Single-use citric acid sachets have been used as an inducement to get heroin users to exchange their dirty needles for clean needles in an attempt to decrease the spread of AIDS and hepatitis.[12] Other acidifiers used for brown heroin are ascorbic acid, acetic acid, and lactic acid; in their absence, a drug user will often substitute lemon juice or vinegar.
- Citric acid is used as one of the active ingredients in the production of antiviral tissues.

Dyeing

Citric acid can be used in food coloring to balance the pH level of a normally basic dye. It is used as an odorless alternative to white vinegar for home dyeing with acid dyes.

Qualitative analysis

Sodium citrate, a conjugate base of citric acid, is used as a chelating agent and is present in the Benedict's reagent, used for identification both qualitatively and quantitatively, of reducing sugars.

6. MATERIALS

INGREDIENTS USED:

S.NO	MATERIALS	SOURCE
1.	Zolmitriptan	Aurobindo
2.	Aerosil	Caboril
3.	Mannitol	Spi Polyous ine
4.	Croscarmellose sodium	DMV International
5.	Sodium Starch glycolate	DMV International
6.	Crosspovidone	BASF
7.	Peppermint Flavour	LUX Flavour
8.	Sucralose	TJTE and LYCE
9.	Magnesium stearate	Sunshine Organics
10	Talc	Luzinac

Table1 materials used for the experiment

FUNCTIONAL CATEGORIES OF EXCIPIENT

Materials	Category
Zolmitriptan	Active Pharmaceutical Ingredient
Mannitol	Diluents
Aerosil	Glidant
Crospovidone	Superdisintegrant
Croscarmellose sodium	Superdisintegrant
Sodium starch glycolate	Superdisintegrant
Sucralose	Sweetener
Peppermint Flavour	Flavour
Magnesium stearate	Lubricant
Talc	Lubricant

Table 2 List of functional category of materials used

LIST OF EQUIPMENTS UTILIZED

INSTRUMENTS	MANUFACTURER
Weighing Balance	Precisa 205A
FTIR	IR Affinity-1 SHIMADZU
Compression Machine	CLIT Single Rotatory 16 Staionary
Hardness tester	Monsanto Hardness Tester-Cadmach
Friabilator	In lab Equipments
Sieves	Sethi Standard Test Sieves
Vernier Calliper	MIUTOYO
UV-Spectrophotometer	Tec comp UV 2300
Dissolution apparatus, U.S.P.	Electrolab Tab. Disso.tester USP–TDT– 06P
Bulk Density Apparatus	VEEGO
HPLC	LC-2010A HT-SHIMADZU
PH meter	Elchem
Disintegration Test Apparatus USP	VEEGO Model-VTD-DV
Magnetic Stirrer	LASCO
Sonicator	Ultra Sonic Agitator-SAISONIC

Table 3 List of Equipments Used

7. METHODOLOGY

7.1 PREFORMULATION STUDIES

Preformulation testing is an investigation of physical and chemical properties of drug substance alone and combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

7.1.1. Compatibility studies by FTIR studies (Fourier transform infrared spectroscopic studies)

In the preparation of ODT tablet, drug and polymer may interact as they are in close contact with each other, which could lead to instability of drug. Preformulation studies regarding drug-polymer interactions are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy (AGILENT TECHNOLOGIES) was employed to ascertain the compatibility between Zolmitriptan and selected polymers. The individual drug and drug with excipients were scanned separately**.**

Procedure:

Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and spectrum was taken using FTIR . FT-IR spectrum of Zolmitriptan was compared with spectrum of Zolmitriptan and polymer. Disappearance of Zolmitriptan peaks or shifting of peak in any of the spectra was studied.

7.2 CHARACTERIZATION OF POWDER [50]

PRECOMPRESSION STUDIES

Prior to compression and blend was evaluated for their characteristic parameters such as:

1. Angle of repose

2. Bulk density

3. Tapped density

4. Compressibility index

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend was measured. The angle of repose was calculated using following formula

Tan □= h/r …… Eqn. (1)

Where, "h" is height of the heap and "r" is the radius of the heap of granules.

Bulk density

Bulk density is used as a measure to describe packing materials or granules. Bulk density is the ratio of given mass of powder and its bulk volume. It was determined by transferring an accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The initial volume was noted. Ratio of weight of the sample to the volume it occupied was calculated.

Bulk density = W/V0 g/ml

W= Mass of the blend

V0 =Untapped volume

Tapped Density:

Tapped density was measured by transferring a known quantity of blend into a graduated cylinder and was placed on the tapped density apparatus. The initial volume was noted. The apparatus was set for 500, 750 and 1250 taps. The tapped density was determined as the ratio of mass of the blend to the tapped volume.

Tapped density=W/V f g/ml

W= Mass of the blend

Vf = Tapped volume

Compressibility index

It is the propensity of a powder to be compressed. It is measured by tapped density apparatus for 500, 750 and 1250 taps for which the difference should be not more than 2%. Based on the apparent bulk density and tapped density the percentage compressibility of the blend was determined using the following formula.

% Compressibility = [(V0 – Vf) / V0] X 100

OR

% Compressibility = [(Tapped density – Bulk density) / Tapped density] X100

7.3 FORMULATION OF TABLETS [51, 52]

DIRECT COMPRESSION

Easiest way to manufacture tablets is direct compression, and advantages of direct compression is

- Cost Effectiveness
- Stability
- Faster Dissolution
- Less wear & tear of punches

However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrants, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrants to ensure quick disintegration and dissolution.

FORMULATION PROCEDURE:

1. Sieve Zolmitriptan, Mannitol through 40mm mesh by geometrical mixing and sieve, Crosscarmellose Sodium, Sucralose, Citric acid, Aerosil, talc, and Peppermint flavor through 40 mesh and add above blend for 5 min.

2. And finally Magnesium Stearate was pass through the 40mm mesh and add to the above blend for 2min.

3. Finally the blend should be compressed in to tablets in single rotator compression machine**s:**

INGREDIENTS(MG)	F-1	F-2	F-3	F-4	F-5	F-6
Zolmitriptan	2.5mg	2.5mg	2.5mg	2.5	2.5	2.5
Mannitol	68.5	58.5mg	72mg	69.5.mg	55.5	68.5
Crosspovidone	-	-	-	-	30	20
Crosscarmellose sodium(CCNA)	-	-	10mg	15mg	-	-
Sodium starch glycolate(SSG)	20mg	25mg	-	-	-	-
Sucralose	2mg	4mg	5mg	4mg	3mg	2mg
Citric acid	1mg	2mg	2mg	1mg	2mg	1mg
Aerosil	2mg	2mg	2mg	3mg	1mg	2mg
Talc	1mg	1mg	1mg	2mg	2mg	1mg
Magnesium stearate	2	4	4mg	2mg	3mg	2mg
Peppermint flavor	1mg	1mg	1mg	1mg	1mg	1mg

Table 4 Formulation of Zolmitriptan Oral disintegration tablets

7.4 POST COMPRESSION STUDIES [53]:

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital Vernier scale and the average thickness was determined in mm. The tablet thickness should be controlled within a ± 3% variation of a standard.

Weight variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

Hardness

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Monsanto hardness tester, Pfizer hardness tester etc.

Friability

It is the measurement of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. A preweighed tablet was placed in the friabilator. Friabilator consist of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets were rotated in the friabilator for at least 4 minutes. At the end of test tablets were dusted and reweighed, the loss in the weight of tablet is the measure of friability and is expressed in percentage as,

$$\% \text{ Friability} = \text{Loss in weight} / \text{Initial weight} \times 100$$

$$\% \text{ Friability} = [(W0 — Wf) / W0] \times 100$$

$$W0 = \text{Initial weight of tablets}$$

W f = Final weight of tablets

$= W_0/W_v/W_0 \times 100.$

7.5 DISINTEGRATION TIME

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 mL which is maintained at 37±2 °C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30 seconds.

7.6 DISSOLUTION STUDIES

Standard preparation

Weigh accurately 25 mg of Standard Zolmitriptan into a 50 mL volumetric flask, dissolve and make up the volume with 0.1N HCl. Transfer 1 mL of the solution into a 100 mL volumetric flask and make up the volume with the 0.1N HCl. The solution contains 5 µg/ mL respectively. Scanned 283 nm by UV spectroscopy.

Test:

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions. The dissolution test was carried out in USP Apparatus Type II (paddle) with 0.1 N Hydrochloric acid as the dissolution medium. The samples were drawn at 5, 10, 15, 20, 30, min. Fresh volume of the medium were replaced with the withdrawn volume to

maintain the sink conditions. Samples withdrawn were analyzed for the percentage of drug released.

Dissolution Parameters:

Dissolution Apparatus	:	USP Apparatus Type II (Paddle)
Dissolution Medium	:	0.1N Hydrochloric acid
Volume	:	500 ml
Temperature	:	37±2° C
Rpm	:	50
Sampling Intervals (min)	:	5, 10, 15, 20, 30 min.

7.7 DRUG CONTENT ESTIMATION [54]

ESTIMATION BY HPLC METHOD

Mobile phase	:	Buffer CH_3OH (750:250).
Buffer	:	750 ml of 0.01M K2HPO4+2ML OF Tri ethylamine.
PH	:	7.5 with H3PO4
Flow Rate	:	1.5 ml/min
Column	:	C18, 150+4.6 M.
X	:	230 nm.
Load	:	20 µl.

STANDARD PREPARATION:

Accurately weigh and transfer 50 mg of Zolmitriptan working standard into a 50 ml volumetric flask add about 25 ml of mobile phase and sonicate to dissolve it completely and make volume up to the mark with the same solvent. Further pipette 5 ml of the above prepared solution into a 50 ml volumetric flask and dilute up to the mark with diluents. Mix well and filter through 0.45 µm filter.

Sample Solution Preparation

Accurately weigh and transfer 50 mg of Zolmitriptan sample powder into a 50 ml volumetric flask add about 25 ml of mobile phase and sonicate to dissolve it completely and make volume up to the mark with the same solvent. Further pipette 5 ml of the above prepared solution into a 50 ml volumetric flask and dilute up to the mark with diluents. Mix well and filter through 0.45µm filter.

KINETIC RELEASE STUDIES

Statistical analysis of the different properties of the formulations was performed, Using the one way analysis of variance (ANOVA), Along with the tucky post test. For this purpose graph Pad instat software version 3.0.1 was used. A statistical significance was defined at $p<0.05$.

Kinetic analysis of in vitro release rates of formulations [55 ,56].

The results in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero-order kinetic model-cumulative percentage drug release versus time.
2. First order kinetic model-log cumulative percentage drug release remaining versus time.
3. Higuchi's model-cumulative percentage drug released versus square root of time
4. Korsmeyer's equation/peppa's model-log cumulative percentage drug released versus log time.

1. Zero-order kinetics

Zero order release would be predicted by the following equation:-

$$A_t = A_0 - K_0 t$$

Where,

A_t=drug release at time ' t'

A_0=Initial drug concentration

K_0=Zero order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero order release kinetics, with a slope equal to k_0.

2. First order kinetics

First order release would be predicted by the following equation:-

$$\text{Log } c = \log c_0 - k_t/2.303$$

Where,

C=amount of drug remained at time t'.

C_0=initial amount of drug

K=first-order rate constant ($^{hr-1}$)

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follows first order kinetics. The constant k can be obtained by multiplying 2.303 with slope values.

3. Higuchi model

Drug release from the matrix devices by diffusion has been described by following higuchi's classical diffusion equation.

$$Q = (D\varepsilon/\tau(2A-\varepsilon C_S)Cst)^{1/2}$$

where,

Q= amount of drug release at time't'

D=diffusion coefficient of drug in the matrix

A=total amount of drug in unit volume of matrix

Cs=the solubility of drug in the matrix

ε=porosity of the matrix

τ=time (hrs) at which Q amount of drug is released

Above equation may be simplified if one assumes that D, Cs, and A, are constant.

Then equation becomes

$$Q = K\, t^{1/2}$$

When the data is plotted according to equation i.e cumulative drug release versus . Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'k'.

4. korsemeyer equation / peppa's model)

Equation/peppas law equation) which is often to describe the drug release behavior from polymeric systems.

$$M_t/M_a = kt^n$$

Where,

M_t/M_a=the fraction of drug released at time 't'

K=constant incorporating the structural and geometrical characteristics of the drug/polymeric.

N=diffusion exponent related to the mechanism of release

Above equation can be simplified by applying log on both sides, and we get:

$$\log M_t/ M_a = \log_k + n \log t$$

When the data is plotted as log of drug release versus log time, yields a straight line with a slope equal to 'n' and the 'k' can be obtained from y-intercept. For Fickian release 'n'=0.5 while for anomalous (non-Fickian) transport 'n' ranges from 0.5 to 1.0 as shown below.

Table: 5 Mechanism of drug release as per Korsemeyer equation/ Peppa's model.

S.No	n Value	Drug release
1.	n<0.5	Fickians release
2.	0.5<n<1	Non fickians release
3.	n>1	Case 11 transport

8. RESULTS

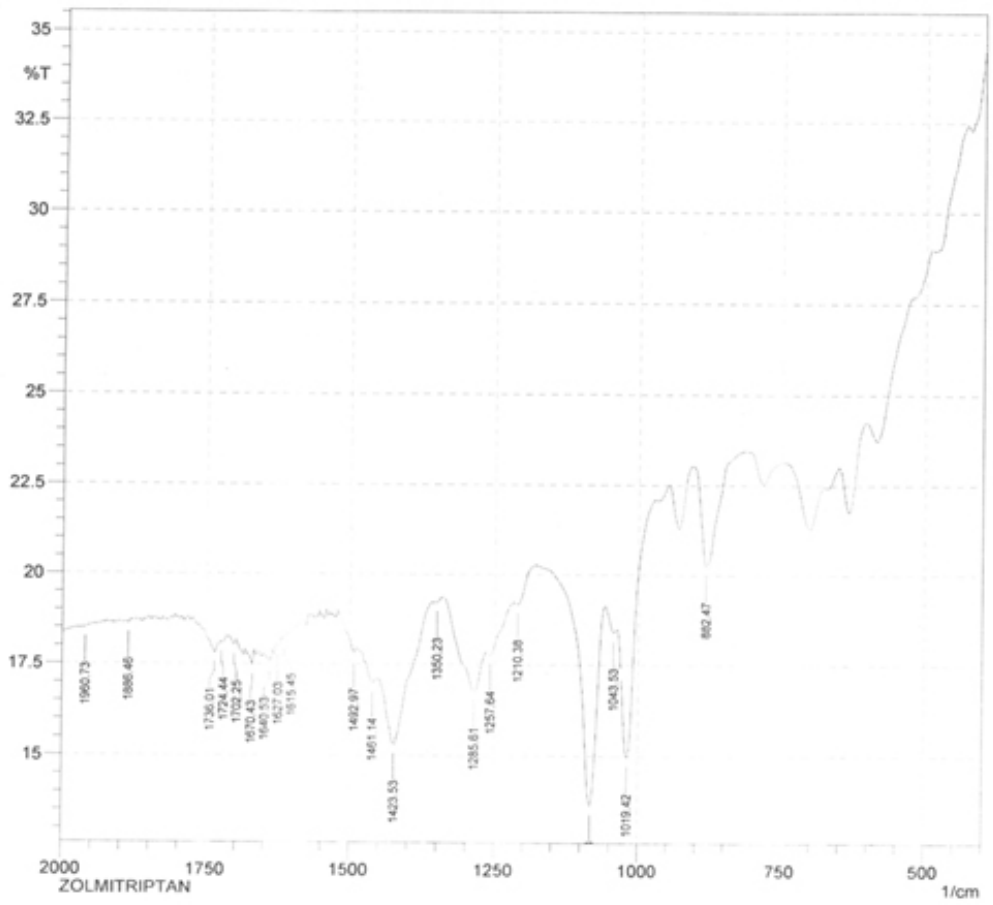
8.1 Preformulation Studies

8.1.1 Compatibility studies (Fourier transform infrared spectroscopic studies)

Potassium Bromide pellet method was used in the study. Test samples were prepared by physical mixing of Zolmitriptan and excipients in ratios of 1:1 Initially.100mg of potassium bromide power was mixed with 2mg of each sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBR pellet was placed in sample holder of Bruker FT-IR spectrophotometer. The spectra were recorded in the wave number region of 4000-500cm-1. In each case the spectra was compared with the pure zolmitriptan spectrum to detect the interactions between drug and excipients.

The FTIR Graphs of drug and excipients were shown in the figures

SHIMADZU



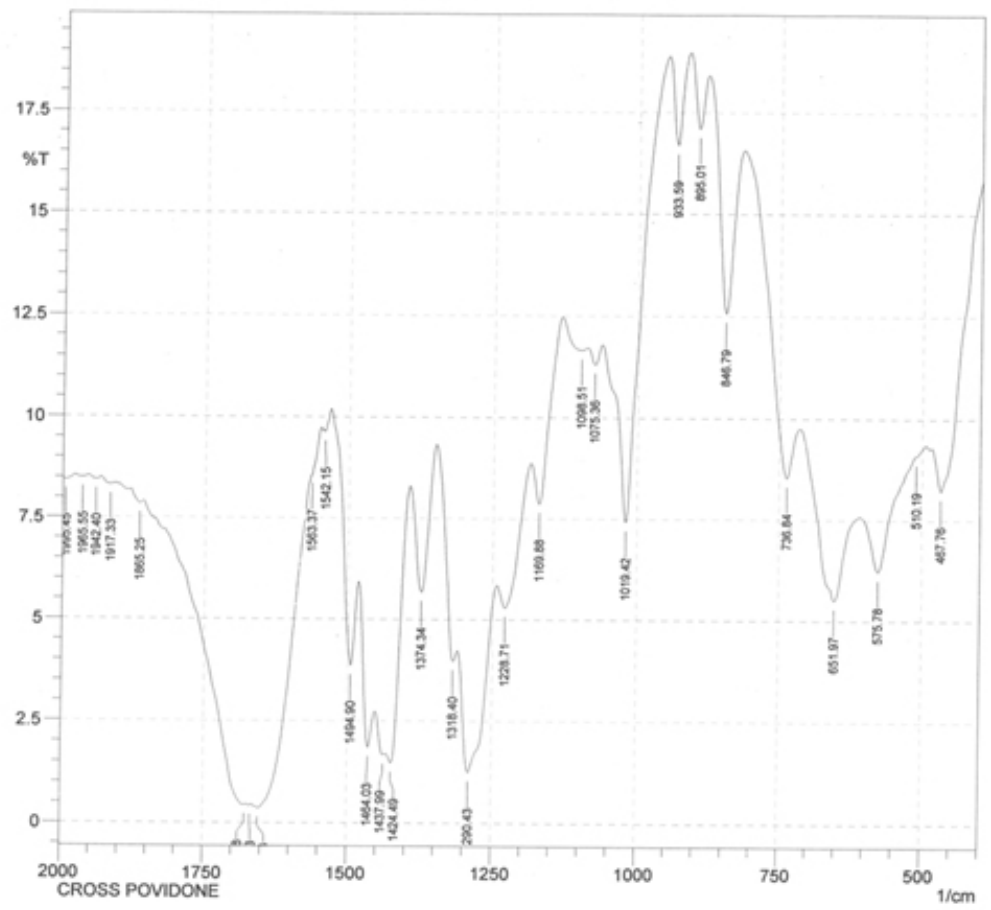
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	882.47	20.246	2.903	906.58	815.92	59.187	1.744
2	1019.42	14.959	4.555	1037.75	973.13	47.002	2.254
3	1043.53	18.405	0.24	1058	1038.71	14.067	0.061
4	1083.08	13.651	5.71	1178.56	1058.97	88.58	4.2
5	1210.38	19.175	0.234	1217.14	1179.52	26.534	0.076
6	1257.64	17.754	0.285	1264.39	1218.1	33.993	0.118
7	1285.61	16.762	1.497	1338.66	1265.36	55.036	1.449
8	1350.23	19.224	0.014	1351.19	1339.62	8.267	0.001
9	1423.53	15.3	2.427	1450.53	1358.91	70.363	2.448
10	1461.14	17.006	0.23	1472.71	1456.32	12.552	0.064
11	1492.97	17.814	0.209	1504.54	1490.07	10.769	0.043
12	1615.45	18.221	0.053	1617.38	1605.81	8.534	0.01
13	1627.03	17.984	0.081	1628.95	1618.35	7.883	0.019
14	1640.53	17.563	0.283	1650.17	1636.67	10.16	0.047
15	1670.43	17.47	0.398	1678.14	1667.53	7.989	0.05
16	1702.25	18.015	0.16	1709.97	1699.36	7.873	0.022
17	1724.44	18.091	0.036	1726.36	1715.76	7.862	0.01
18	1736.01	17.805	0.348	1749.51	1726.36	17.234	0.086
19	1886.46	18.621	0.056	1891.29	1878.75	9.138	0.005
20	1960.73	18.49	0.01	1961.69	1950.12	8.471	0.001

Comment;
ZOLMITRIPTAN

Date/Time; 9/24/2013 11:02:36 AM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 5: FTIR Spectrum of Zolmitriptan

SHIMADZU



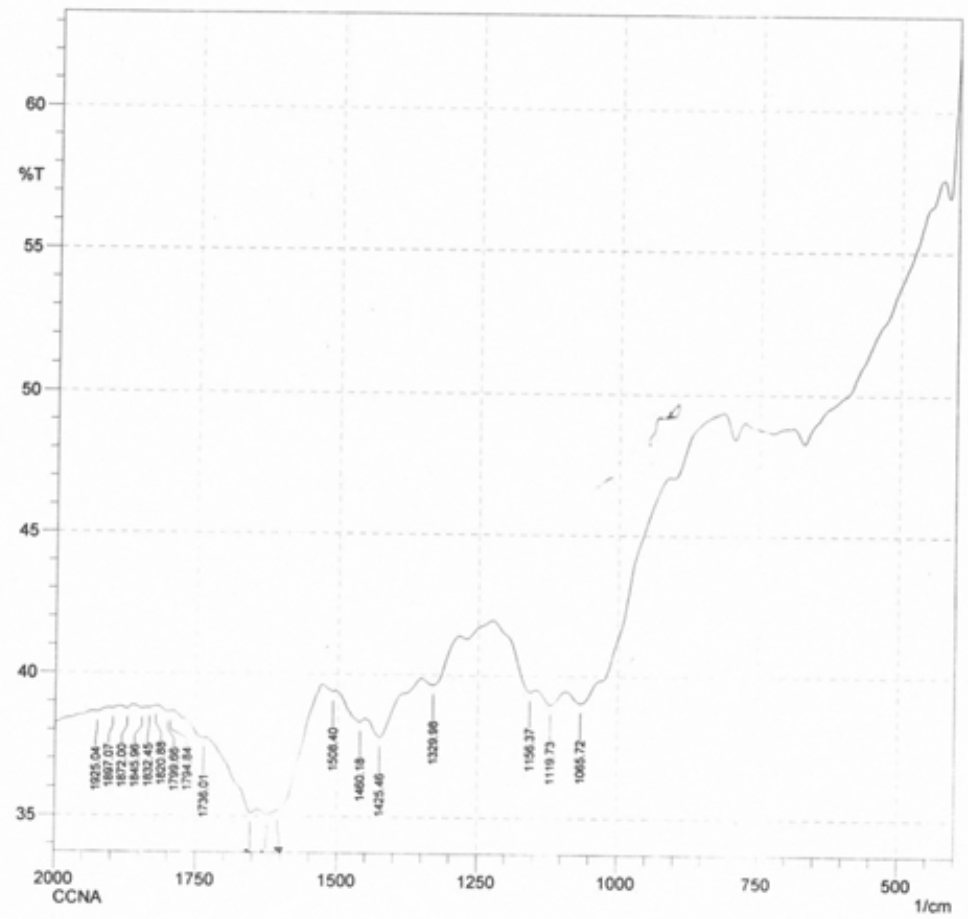
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	467.76	8.235	2.257	483.19	399.28	80.484	3.811
2	510.19	9.079	0.018	511.16	496.69	14.987	0.009
3	575.78	6.222	1.853	606.64	513.09	104.857	3.754
4	651.97	5.507	2.983	713.69	607.6	121.735	8.65
5	736.84	8.542	2.703	815.92	714.66	93.798	3.484
6	846.79	12.574	4.874	879.58	816.89	51.22	3.692
7	895.01	17.098	1.579	912.37	880.54	23.77	0.589
8	933.59	16.692	2.243	949.02	913.33	26.663	0.879
9	1019.42	7.428	7.099	1062.82	949.98	102.427	9.437
10	1075.36	11.315	0.438	1087.9	1063.79	22.627	0.208
11	1098.51	11.663	0.223	1132.26	1088.86	40.193	0.355
12	1169.88	7.874	2.015	1184.34	1133.23	51.784	1.895
13	1228.71	5.294	1.272	1242.21	1185.31	67.534	2.656
14	1290.43	1.252	3.441	1309.72	1243.18	105.562	18.872
15	1318.4	3.973	1.276	1349.26	1310.69	47.314	1.202
16	1374.34	5.679	3.091	1394.59	1350.23	50.845	4.041
17	1424.49	1.483	1.735	1433.17	1395.56	55.426	2.959
18	1437.99	1.673	0.252	1451.5	1434.14	29.579	0.558
19	1464.03	1.855	2.153	1481.39	1452.46	44.476	3.957
20	1494.9	3.864	3.134	1532.51	1482.36	59.424	3.938
21	1542.15	9.635	0.083	1543.12	1533.47	9.697	0.03
22	1563.37	8.55	0.074	1564.34	1548.91	16.013	0.012
23	1654.03	0.364	0.96	1664.64	1566.27	171.289	7.776
24	1667.53	0.427	0.024	1673.32	1665.6	18.219	0.131
25	1677.18	0.442	0.144	1821.84	1674.28	226.743	0.691
26	1865.25	7.853	0.137	1880.68	1859.46	23.329	0.11
27	1917.33	8.311	0.065	1933.72	1912.5	22.865	0.055
28	1942.4	8.438	0.071	1953.97	1934.69	20.688	0.049
29	1965.55	8.494	0.005	1966.51	1956.87	10.321	0.004
30	1995.45	8.435	0.039	2000.27	1979.05	22.746	0.03

Comment;
CROSS POVIDONE

Date/Time; 9/17/2013 12:48:31 PM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 6: FTIR Spectrum of Crosspovidone

SHIMADZU



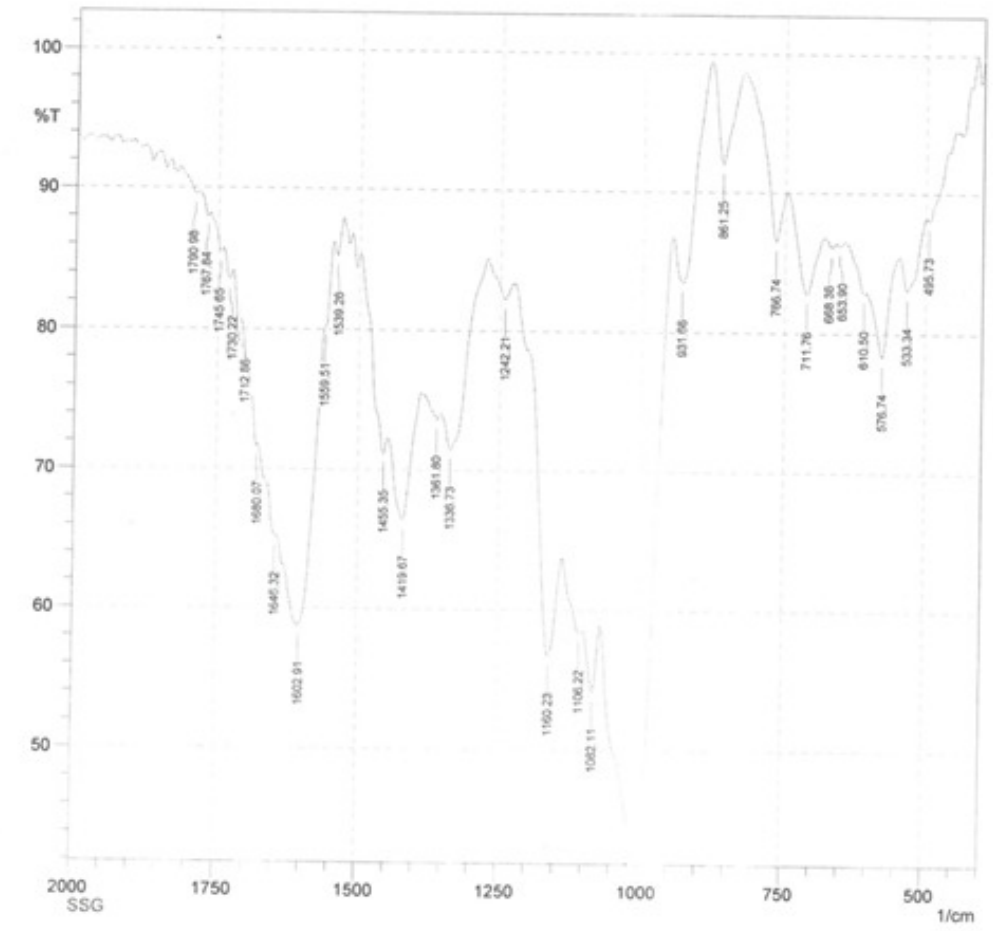
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	1065.72	39.04	1.526	1091.76	910.44	68.057	1.913
2	1119.73	38.992	0.499	1144.8	1092.72	21.161	0.146
3	1156.37	39.446	0.391	1223.89	1145.77	30.537	0.117
4	1329.98	39.655	0.686	1350.23	1284.65	25.895	0.249
5	1425.46	37.811	1.001	1451.5	1351.19	41.227	0.387
6	1460.18	38.338	0.028	1462.11	1452.46	4.011	0.002
7	1508.4	39.387	0.079	1528.65	1505.51	9.337	0.009
8	1604.84	35.199	0.115	1606.77	1529.62	33.138	0.204
9	1623.17	35.067	0.029	1625.1	1606.77	8.327	0.006
10	1653.07	35.112	0.451	1731.19	1641.49	39.387	0.121
11	1736.01	37.719	0.087	1770.73	1732.15	16.213	0.035
12	1794.84	38.649	0.005	1795.8	1791.95	1.592	0
13	1799.66	38.639	0.031	1816.06	1797.73	7.551	0.005
14	1820.88	38.841	0.004	1821.84	1817.02	1.98	0
15	1832.45	38.785	0.011	1834.38	1822.81	4.757	0.001
16	1845.96	38.755	0.055	1860.42	1841.13	7.93	0.005
17	1872	38.751	0.102	1885.5	1861.39	9.912	0.012
18	1897.07	38.756	0.041	1904.79	1886.46	7.537	0.003
19	1925.04	38.635	0.043	1931.79	1905.75	10.738	0.006

Comment;
CCNA

Date/Time; 9/24/2013 11:34:53 AM
No. of Scans;
Resolution;
Apodization;
User: A

Figure 7: FTIR Spectrum of Croscarmellose Sodium

SHIMADZU



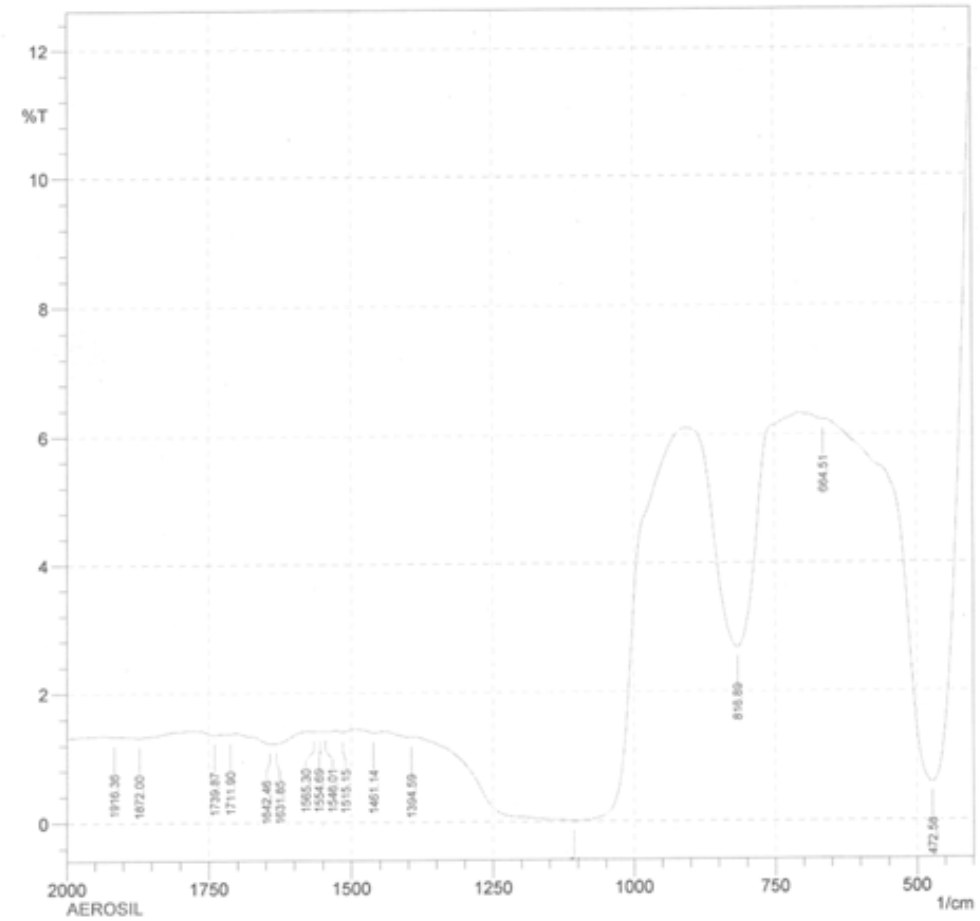
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	495.73	88.114	0.646	499.58	461.97	1.721	0.125
2	533.34	83.087	3.19	546.84	500.55	3.283	0.455
3	576.74	78.395	5.813	606.64	547.81	5.135	0.741
4	610.5	82.85	0.353	643.29	607.6	2.571	0.017
5	653.9	86.244	0.188	659.68	644.25	0.984	0.009
6	668.36	86.087	0.445	679.94	660.65	1.228	0.019
7	711.76	82.748	5.574	745.52	680.9	4.372	0.897
8	766.74	86.512	5.764	824.6	746.48	2.632	0.643
9	861.25	92.024	7.149	882.47	825.57	1.123	0.889
10	931.66	83.546	6.44	948.05	883.44	3.105	1.069
11	1012.67	44.642	27.31	1068.61	949.02	31.421	14.087
12	1082.11	54.167	4.586	1100.44	1069.57	7.684	0.549
13	1106.22	58.35	0.859	1137.09	1101.4	7.848	0.184
14	1160.23	56.72	11.963	1225.82	1138.05	14.091	2.207
15	1242.21	82.242	1.735	1272.11	1226.78	3.59	0.21
16	1336.73	71.471	4.94	1354.09	1273.07	9.065	1.007
17	1361.8	73.651	0.691	1387.84	1355.05	4.195	0.055
18	1419.67	66.435	7.424	1447.64	1388.81	9.057	1.346
19	1455.35	71.165	2.878	1498.75	1448.6	5.699	0.414
20	1539.26	85.248	1.73	1546.98	1529.62	1.109	0.069
21	1559.51	80.211	0.479	1560.48	1547.94	1.024	0.035
22	1602.91	58.757	13.757	1642.46	1560.48	15.62	4.163
23	1646.32	65.144	0.739	1677.18	1643.42	5.624	0.071
24	1680.07	71.695	0.674	1691.64	1678.14	1.822	0.036
25	1712.86	80.423	0.908	1724.44	1709.97	1.273	0.046
26	1730.22	83.461	1.144	1740.83	1725.4	1.151	0.049
27	1745.65	85.408	0.688	1763.98	1741.8	1.379	0.025
28	1767.84	87.975	0.415	1786.16	1764.94	1.088	0.016
29	1790.98	89.522	0.423	1817.99	1787.12	1.345	0.018

Comment;
SSG

Date/Time: 9/24/2013 11:15:40 AM
No. of Scans:
Resolution:
Apodization:
User:

Figure 8: FTIR Spectrum of Sodium Starch Glycolate

SHIMADZU



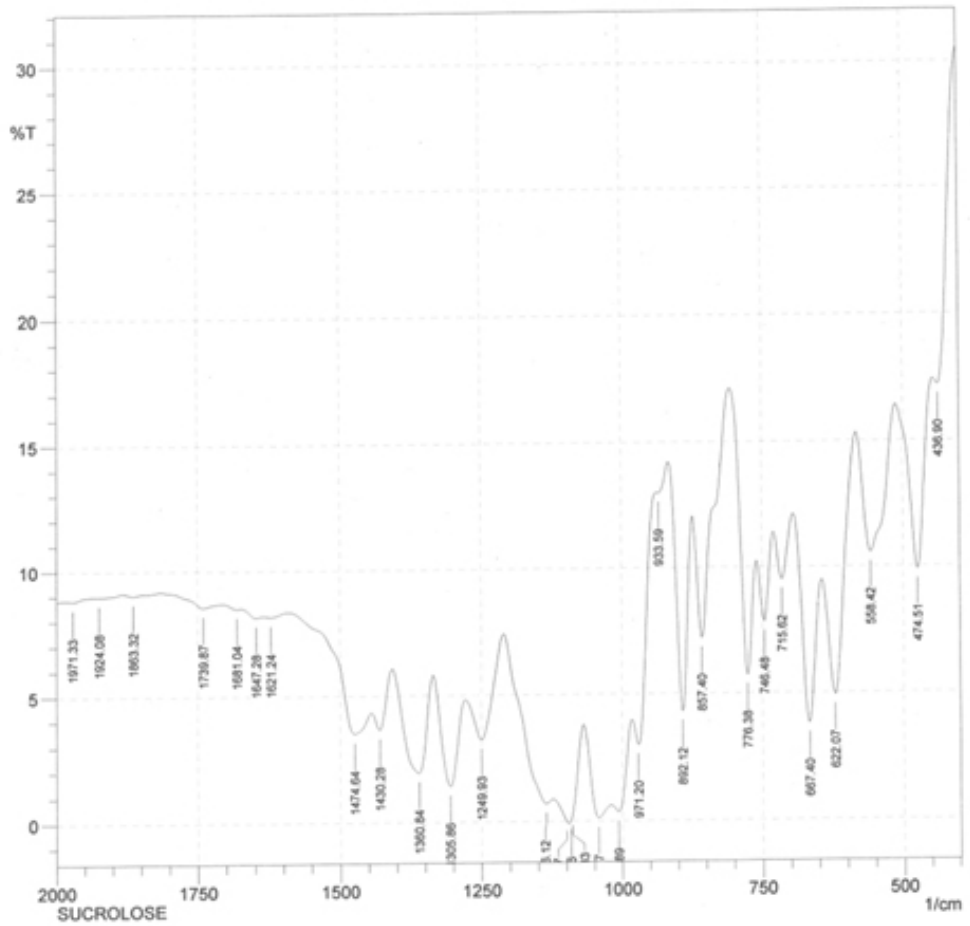
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	472.58	0.587	9.808	661.61	399.28	379.82	101.085
2	664.51	6.226	0.006	705.01	662.58	51.019	0.009
3	816.89	2.681	3.524	906.58	705.98	266.608	24.59
4	1106.22	0.009	4.115	1387.84	907.55	1186.017	443.742
5	1394.59	1.311	0.012	1440.89	1388.81	97.462	0.21
6	1461.14	1.382	0.037	1490.07	1441.85	89.335	0.259
7	1515.15	1.394	0.032	1528.65	1491.04	69.548	0.158
8	1546.01	1.403	0.005	1551.8	1529.62	41.072	0.028
9	1554.69	1.404	0.001	1557.59	1552.76	8.934	0.001
10	1565.3	1.402	0.006	1574.95	1558.55	30.368	0.013
11	1631.85	1.223	0.013	1635.71	1575.91	112.453	0.152
12	1642.46	1.221	0.019	1672.36	1636.67	67.77	0.156
13	1711.9	1.37	0.006	1718.65	1701.29	32.322	0.014
14	1739.87	1.356	0.034	1781.34	1719.61	114.666	0.23
15	1872	1.316	0.045	1907.68	1782.3	234.077	0.854
16	1916.36	1.334	0.005	1934.69	1908.65	48.788	0.02

Comment;
AEROSIL

Date/Time; 9/17/2013 12:34:18 PM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 9: FTIR Spectrum of Aerosil

SHIMADZU



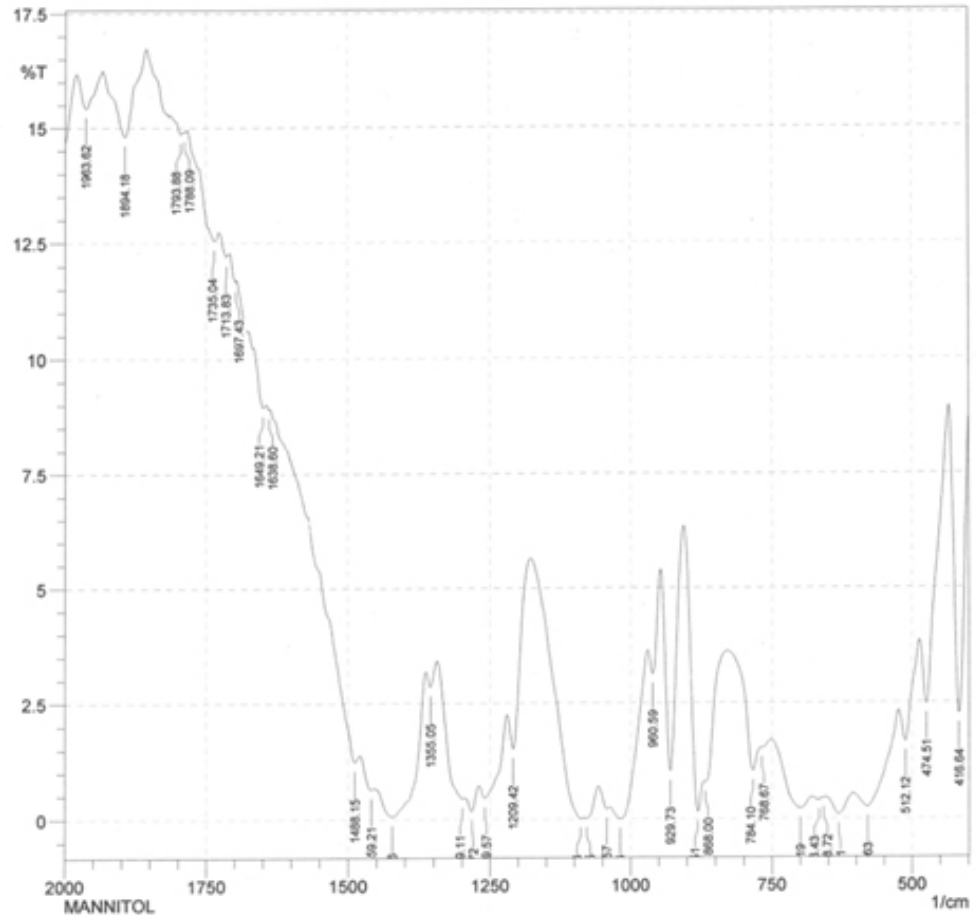
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	436.9	17.208	2.444	444.61	399.28	29.629	1.103
2	474.51	9.873	7.112	512.12	445.58	57.407	6.057
3	558.42	10.555	5.138	582.53	513.09	62.299	6.766
4	622.07	4.918	6.682	644.25	583.49	64.632	8.882
5	667.4	3.808	6.853	694.4	645.22	56.714	8.942
6	715.62	9.509	2.154	729.12	695.37	32.907	1.504
7	746.48	7.842	2.873	759.02	730.09	29.873	1.904
8	776.38	5.73	6.987	805.32	759.99	45.3	5.483
9	857.4	7.195	6.016	872.83	806.28	62.303	6.283
10	892.12	4.308	8.684	915.26	873.79	44.872	8.193
11	933.59	12.974	0.181	936.48	916.23	17.674	0.131
12	971.2	2.999	3.113	981.81	937.44	53.268	3.681
13	1006.89	0.357	1.457	1020.39	982.77	74.979	7.674
14	1042.57	0.111	1.925	1068.61	1021.35	104.93	18.717
15	1089.83	0.104	0.168	1090.79	1069.57	38.178	0
16	1091.76	0	0.034	1092.72	1091.76	3.351	0
17	1099.47	0	-0.015	1100.44	1098.51	385.78	94.61
18	1136.12	0.694	1.06	1210.38	1124.55	140.336	5.289
19	1249.93	3.248	2.658	1277.9	1211.35	89.252	7.906
20	1305.86	1.424	3.863	1334.8	1278.86	85.894	14.407
21	1360.84	1.951	3.942	1407.13	1335.76	105.607	18.039
22	1430.28	3.655	1.357	1444.75	1408.1	49.474	2.261
23	1474.64	3.508	1.618	1590.38	1445.71	176.792	4.366
24	1621.24	8.161	0.08	1633.78	1591.34	46.017	0.087
25	1647.28	8.144	0.157	1672.36	1634.74	40.717	0.156
26	1681.04	8.497	0.058	1704.18	1673.32	32.93	0.047
27	1739.87	8.555	0.294	1814.13	1705.15	114.791	0.482
28	1863.32	9.036	0.103	1881.64	1815.09	69.272	0.16
29	1924.08	8.988	0.006	1926.01	1882.61	45.315	0.051
30	1971.33	8.824	0.06	1984.84	1926.97	60.756	0.048

Comment;
SUCROLOSE

Date/Time; 9/17/2013 12:37:15 PM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 10: FTIR Spectrum of Sucrose

SHIMADZU



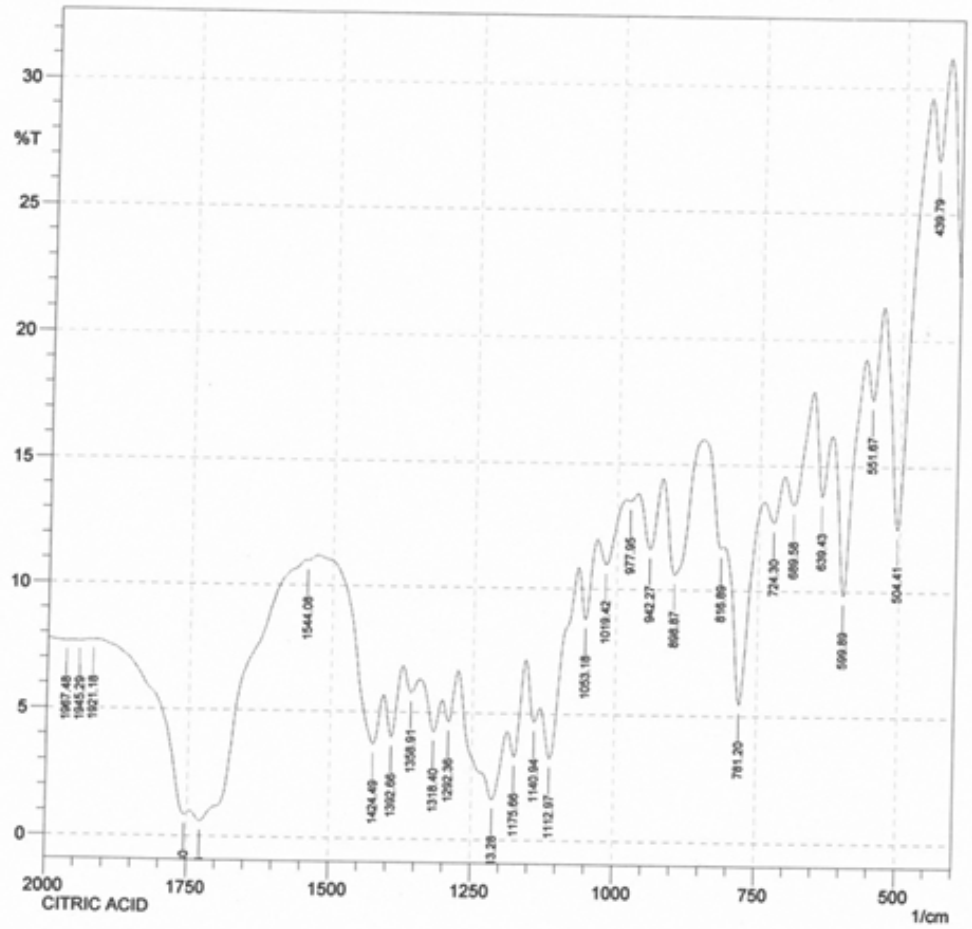
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	416.64	2.258	6.604	434	399.28	45.917	9.37
2	474.51	2.472	2.522	486.08	434.97	67.47	4.681
3	512.12	1.667	1.139	523.7	487.05	58.972	3.228
4	579.63	0.255	0.86	605.67	524.66	176.189	18.463
5	631.71	0.089	0.411	654.86	606.64	124.776	13.823
6	658.72	0.441	0.009	660.65	655.83	11.325	0.026
7	666.43	0.404	0.006	667.4	660.65	16.028	0.025
8	700.19	0.224	0.617	751.31	678.01	165.528	15.23
9	768.67	1.53	0.01	769.63	752.27	31.143	0.069
10	784.1	1.036	0.983	828.46	770.6	95.696	3.201
11	868	0.798	0.14	869.93	829.43	67.379	0.457
12	881.51	0.161	2.333	905.62	870.9	65.94	9.036
13	929.73	1.036	4.768	947.09	906.58	61.222	11.325
14	960.59	3.127	1.217	969.27	948.05	30.209	1.545
15	1018.46	0.004	1.184	1036.78	970.24	165.878	32.828
16	1042.57	0.219	0.149	1057.04	1037.75	47.293	1.418
17	1078.25	0.021	0.117	1082.11	1058	69.694	3.014
18	1088.86	0.013	0.361	1177.59	1083.08	186.12	2.73
19	1209.42	1.522	1.53	1219.06	1178.56	61.286	3.384
20	1259.57	0.462	0.562	1269.22	1220.03	101.769	8.875
21	1282.72	0.176	0.414	1294.29	1270.18	58.858	5.036
22	1299.11	0.447	0.252	1343.48	1295.26	95.207	3.704
23	1355.05	2.856	0.422	1362.77	1344.44	27.708	0.563
24	1422.56	0.063	1.476	1453.43	1363.73	215.816	51.644
25	1459.21	0.648	0.168	1478.5	1454.39	49.914	1.223
26	1488.15	1.244	0.64	1570.12	1479.47	135.61	1.298
27	1638.6	8.911	0.046	1642.46	1636.67	6.07	0.009
28	1649.21	8.954	0.402	1664.64	1643.42	21.836	0.23
29	1697.43	11.66	0.146	1707.08	1695.5	10.724	0.054
30	1713.83	12.208	0.101	1727.33	1711.9	13.976	0.034
31	1735.04	12.545	0.236	1745.65	1728.29	15.591	0.087
32	1788.09	14.902	0.031	1790.02	1784.23	4.781	0.004
33	1793.88	14.863	0.11	1813.16	1790.98	18.239	0.026
34	1894.18	14.803	1.698	1933.72	1856.57	62.119	1.736
35	1963.62	15.428	0.78	1980.01	1934.69	36.332	0.521

Comment;
MANNITOL

Date/Time; 9/17/2013 12:53:39 PM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 11: FTIR Spectrum of Mannitol

SHIMADZU



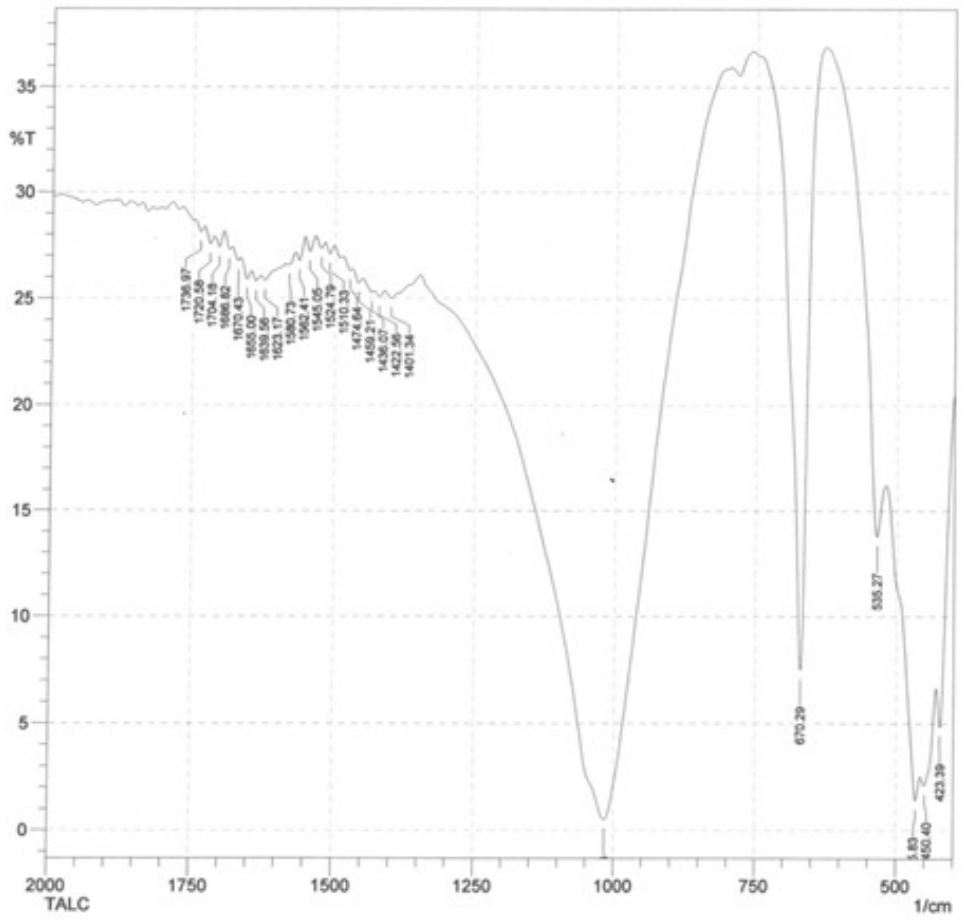
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	439.79	27.084	3.228	454.26	421.46	17.706	0.759
2	504.41	12.501	11.93	534.3	455.22	55.846	8.445
3	551.67	17.647	2.479	564.2	535.27	20.904	0.848
4	599.89	9.851	7.565	623.03	565.17	49.035	5.488
5	639.43	13.781	3.255	655.83	624	25.899	1.418
6	689.58	13.434	2.275	705.98	656.79	40.531	1.676
7	724.3	12.723	1.343	741.66	706.94	30.328	0.757
8	781.2	5.478	7.051	811.1	742.63	70.14	8.594
9	816.89	11.663	0.609	850.64	812.07	33.255	0.284
10	898.87	10.61	4.324	921.05	851.61	61.82	5.027
11	942.27	11.604	2.533	964.45	922.01	37.861	1.792
12	977.95	13.527	0.133	984.7	965.41	16.7	0.05
13	1019.42	10.991	1.491	1034.85	985.67	45.151	1.203
14	1053.18	8.792	2.543	1066.68	1035.82	30.689	1.595
15	1112.97	3.265	3.516	1130.33	1067.65	76.39	6.128
16	1140.94	4.681	1.272	1156.37	1131.3	31.823	1.299
17	1175.66	3.32	2.065	1187.24	1157.34	40.307	2.826
18	1213.28	1.619	3.355	1275.97	1188.2	133.247	21.569
19	1292.36	4.651	1.315	1302.97	1276.93	33.106	1.417
20	1318.4	4.247	1.545	1343.48	1303.94	50.844	2.182
21	1358.91	5.78	0.783	1373.38	1344.44	35.066	0.814
22	1392.66	4.023	2.153	1407.13	1374.34	42.308	2.788
23	1424.49	3.745	2.672	1526.72	1408.1	133.368	6.231
24	1544.08	10.982	0.032	1546.98	1527.69	18.44	0.017
25	1727.33	0.606	1.267	1744.69	1547.94	273.61	10.277
26	1755.3	0.858	0.516	1914.43	1745.65	225.212	1.224
27	1921.18	7.698	0.002	1926.01	1915.4	11.813	0.001
28	1945.29	7.65	0.03	1955.9	1926.97	32.266	0.023
29	1967.48	7.654	0.037	2000.27	1956.87	48.358	0.068

Comment;
CITRIC ACID

Date/Time; 3/14/2013 9:58:28 AM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 12: FTIR Spectrum of Citric Acid

SHIMADZU



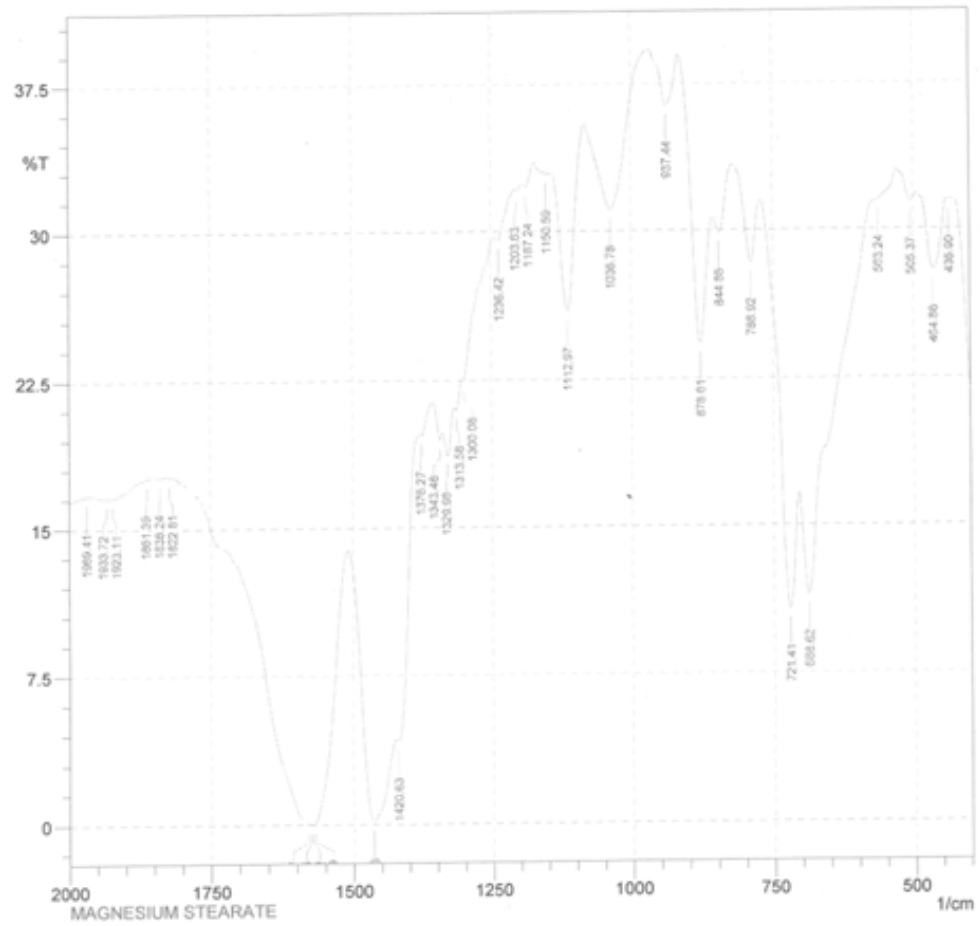
No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	423.39	4.846	4.825	430.14	399.28	30.559	2.355
2	450.4	2.108	1.469	457.15	431.11	39.101	3.118
3	465.83	1.407	2.812	519.84	458.11	72.464	2.953
4	535.27	13.789	5.211	627.86	520.8	62.377	1.728
5	670.29	7.503	29.342	758.06	628.82	74.157	18.065
6	1016.53	0.507	31.525	1349.26	797.6	478.96	195.511
7	1401.34	25.028	0.468	1412.92	1350.23	37.25	0.29
8	1422.56	25.079	0.276	1431.24	1413.88	10.387	0.041
9	1436.07	25.295	0.161	1452.46	1432.21	12.009	0.031
10	1459.21	25.724	0.356	1469.82	1453.43	9.608	0.053
11	1474.64	26.324	0.217	1486.22	1470.79	8.887	0.03
12	1510.33	27.104	0.457	1518.04	1502.61	8.697	0.059
13	1524.79	27.354	0.383	1534.44	1519.01	8.642	0.054
14	1545.05	27.198	0.716	1552.76	1535.4	9.721	0.101
15	1562.41	26.779	0.72	1570.12	1553.73	9.281	0.098
16	1580.73	26.574	0.106	1582.66	1571.09	6.622	0.02
17	1623.17	25.856	0.299	1629.92	1588.45	24.098	0.073
18	1639.56	25.817	0.367	1646.32	1630.88	9.033	0.047
19	1655	25.922	0.625	1665.6	1647.28	10.645	0.1
20	1670.43	26.77	0.291	1681.04	1666.57	8.228	0.04
21	1686.82	27.314	0.369	1695.5	1682	7.55	0.036
22	1704.18	27.428	0.621	1712.86	1696.47	9.135	0.083
23	1720.58	27.57	0.541	1730.22	1713.83	9.095	0.066
24	1736.97	28.132	0.362	1746.62	1731.19	8.451	0.045

Comment;
TALC

Date/Time; 3/14/2013 10:09:01 AM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 13: FTIR Spectrum of Talc

SHIMADZU

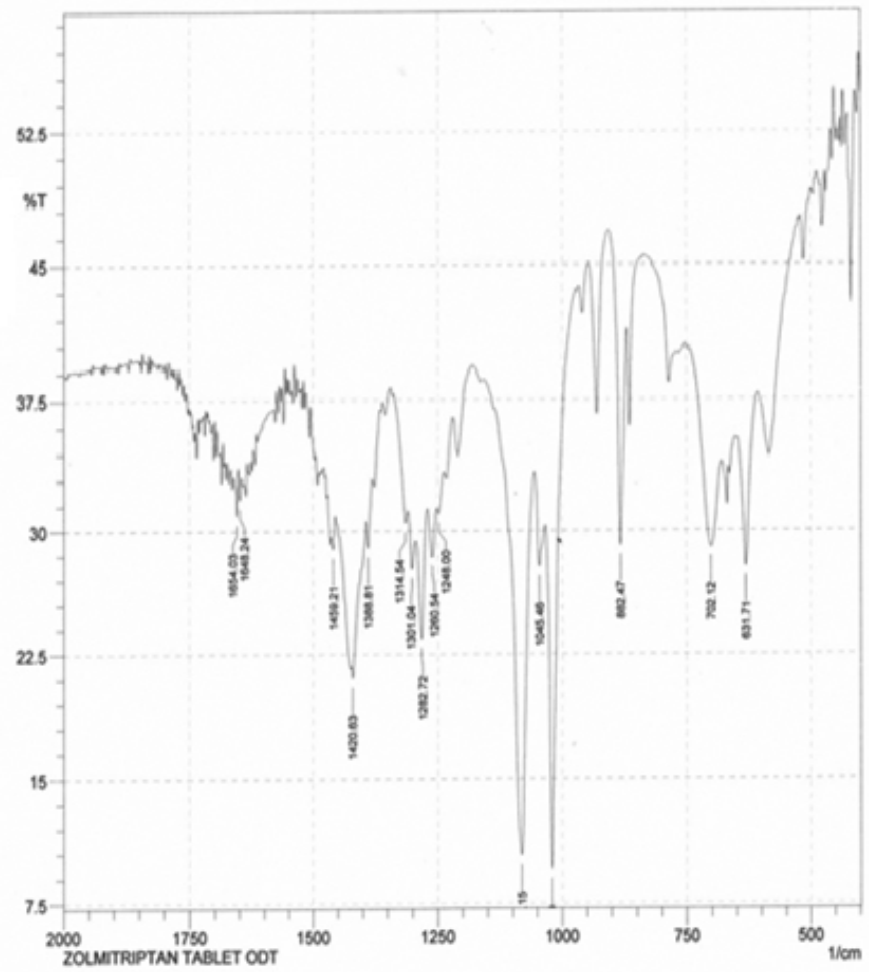


No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	436.9	31.408	0.103	439.79	432.07	3.875	0.005
2	464.86	27.918	3.646	487.05	440.75	24.504	1.319
3	505.37	31.351	0.787	529.48	495.73	16.662	0.136
4	563.24	31.472	0.047	564.2	530.45	16.701	0.115
5	688.62	11.456	6.91	705.01	564.2	94.452	5.096
6	721.41	10.718	9.4	771.56	705.98	46.845	5.072
7	788.92	28.363	3.749	819.78	772.52	24.161	1.008
8	844.86	29.873	1.567	855.47	820.75	17.525	0.345
9	878.61	24.272	9.493	915.26	856.43	30.572	3.38
10	937.44	36.362	2.714	968.31	916.23	22.008	0.77
11	1036.78	31.095	5.864	1081.15	969.27	51.605	3.73
12	1112.97	25.973	8.11	1139.98	1082.11	30.054	3.065
13	1150.59	32.921	0.081	1171.81	1147.69	11.586	0.039
14	1187.24	32.259	0.507	1193.99	1172.77	10.303	0.081
15	1203.63	32.082	0.119	1206.53	1194.95	5.695	0.012
16	1236.42	29.547	0.606	1243.18	1207.49	18.268	0.098
17	1300.08	22.456	0.426	1302.97	1244.14	33.906	0.04
18	1313.58	21.006	0.49	1317.44	1303.94	8.993	0.073
19	1329.98	18.661	1.619	1337.69	1318.4	13.659	0.357
20	1343.48	19.506	0.742	1355.05	1338.66	11.404	0.129
21	1376.27	19.72	0.16	1378.2	1356.02	15.204	0.024
22	1420.63	4.217	1.135	1423.53	1382.06	41.526	1.034
23	1464.03	0.126	8.66	1508.4	1424.49	138.645	45.038
24	1568.19	0.038	0.223	1569.16	1509.36	88.202	0
25	1570.12	0	0.012	1571.09	1570.12	3.797	0
26	1574.95	0	0.003	1575.91	1573.98	385.78	94.525
27	1579.77	0.024	0.286	1718.65	1576.87	209.965	0.196
28	1822.81	17.652	0.028	1826.67	1819.92	5.084	0.003
29	1838.24	17.638	0.043	1844.03	1830.52	10.169	0.01
30	1861.39	17.608	0.012	1862.35	1852.71	7.268	0.003
31	1923.11	16.612	0.042	1925.04	1863.32	47.383	0.08
32	1933.72	16.587	0.023	1936.61	1926.01	8.274	0.004
33	1969.41	16.689	0.004	1970.37	1961.69	6.747	0.001

Comment;
MAGNESIUM STEARATE

Date/Time; 9/17/2013 12:15:39 PM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 14: FTIR Spectrum of Magnesium Stearate



SHIMADZU

No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	A	rea	Corr. Are
1	631.71	27.845	8.528	648.11	607.6	1		
2	702.12	29.013	7.151	743.59	680.9	2	7.295	1.623
3	882.47	29.118	13.934	907.55	870.9	1	9.607	2.541
4	1020.39	9.564	23.665	1033.89	972.16	3	1.842	1.793
5	1045.46	27.841	4.09	1055.11	1034.85	1	3.95	6.152
6	1081.15	10.409	24.141	1136.12	1056.07	4	0.645	0.552
7	1248	31.058	0.874	1251.86	1237.39	7	3.154	11.804
8	1260.54	28.423	2.926	1270.18	1252.82		9.147	0.081
9	1282.72	23.434	6.917	1294.29	1271.14	1	1.117	0.371
10	1301.04	27.697	2.46	1308.76	1295.26	7	3.122	1.144
11	1314.54	30.504	1.807	1338.66	1309.72	1	1.263	0.243
12	1388.81	28.975	2.349	1392.66	1381.09	5	3.602	0.194
13	1420.63	21.08	1.291	1422.56	1393.63	1	1.914	0.163
14	1459.21	28.905	1.398	1463.07	1455.35	4	3.983	0.149
15	1648.24	31.904	1.46	1651.14	1645.35	2	2.082	0.09
16	1654.03	30.914	2.657	1660.78	1652.1	4	4.831	0.069
							1.253	0.123

Comment;
ZOLMITRIPTAN TABLET ODT

Date/Time; 3/14/2013 9:43:46 AM
No. of Scans;
Resolution;
Apodization;
User; A

Figure 15: FTIR Spectrum of Zolmitriptam Oral Disintegration Tablet

Standard calibration curve of zolmitriptan[54]:

Weigh 50 mg of pure drug Zolmitriptan and is dissolved in 0.1N HCL solution and from this solution the series concentrations prepared (4,8,12,16,20 µg/ml) and absorbance is noted at 267nm.

S.no	Concentration(µg/ml)	Absorbance
1	0	0
2	1	0.152
3	2	0.286
4	4	0.572
5	6	0.865
6	8	1.119

Table 6: Standard calibration curve values of Zolmitriptan

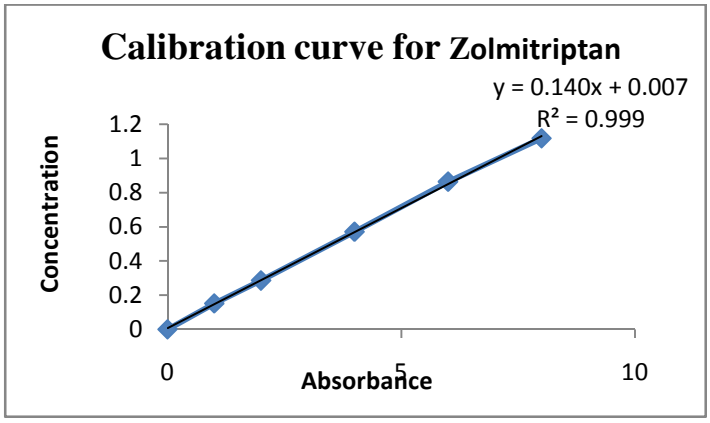


Fig 16 Standard Calibration Curve of Zolmitriptan

Preformulation studies

Table7: Pre formulation evaluation parameters of all the formulations of Zolmitriptan

S.No	Formulation	Angle of repose(^{0}) ±SD	Bulk Density (g/ml)±SD	Tapped Density (g/m) ±SD	Carr's index ± SD
1	F1	27^0.54±0.04	0.49±0.03	0.56±0.03	15.69
2	F2	27^0.38 ±0.06	0.53±0.04	0.57±0.01	16.28
3	F3	29^0.73±0.09	0.45±0.01	0.54±0.03	16.28
4	F4	26^0.66±0.36	0.49±0.01	0.52±0.02	15.18
5	F5	26°.85'± 0.24	0.47±0.02	0.90±0.03	47.63
6	F6	26°.08'±'0.36	0.43±0.01	0.76±0.02	43.42

From the above pre compression parameters the blends showed good flow properties and the excepients didn't show any effect.

Post formulation studies

Table 8: post formulation evaluations of all the formulation of Zolmitriptan

S.No	Formulation	Weight variation test(gm)	Thickness test (mm)	Hardness test (Kg/Cm^2)	Friability test (%)	Disintegrating Time (sec)
1	F1	0.646±3	2.0±0.02	2.9	0.27	53±2
2	F2	0.701±2	1.8±0.02	2.5	0.4	45±3
3	F3	0.765±4	1.8±0.02	2.6	0.37	47±4
4	F4	0.684±2	1.9±0.01	2.3	0.46	43±2
5	F5	0.102±4	2.97±0.01	4	2.4	20±3
6	F6	0.097±3	2.95±0.01	3.5	2.8	15±4

From the above post compression parameters of all the six formulations are found to be within the limit

DISINTEGRATION TEST:

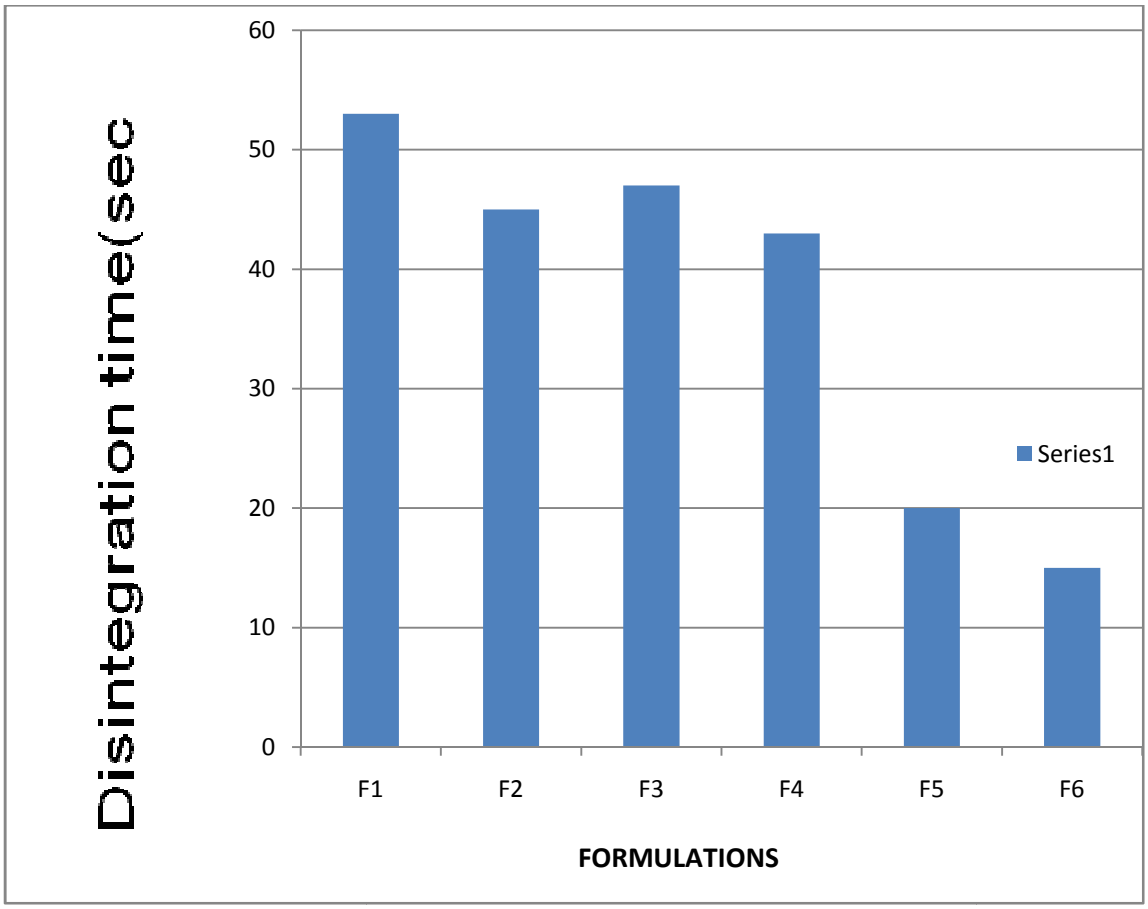


Fig17: The disintegration time of Zolmitriptan formulations:

DISSOLUTION TEST:

Table 9: In vitro drug release of (F1) Zolmitriptan

TIME(Min)	Trail 1	Trail 2	Trail 3	Mean	±S.D
0	0	0	0	0	0
5	56.3	53.6	53.2	54.36	1.686
10	68.7	67.9	69.2	68.6	0.655
15	72.9	73.9	74.8	73.86	0.950
30	79.6	80.1	80.8	80.16	0.602

N=3 Each value represents the mean ± S.D of three experiments

Table 10: Percentage drug release formulation of Zolmitriptan oral disintegrating tablet

Time	Absorbance (nm)	Concentration	Amount of drug release	Amount of drug release/500	Cumulative drug release	% Drug release
0	0	0	0	0	0	0
5	0.019	0.135	0.002	1.35	1.35	54.39

10	0.024	0.171	0.0034	1.71	1.71	68.68
15	0.026	0.185	0.003	1.85	1.86	74.42
30	0.028	0.2	0.004	2	2.00	80.16

N=3 Each value represents the mean ± S.D of three experiments

Table 11: Kinetic drug release formulation of Zolmitriptan oral disintegrating tablet

Square root	**Log time**	**% Drug release**	**log% Drug release**	**% Drug remaining**	**log % Drug remaining**
2.236	0.69	54.3	1.7	45.7	1.65
3.162	1	68.6	1.83	31.4	1.49
3.872	1.17	74.4	1.87	25.6	1.40
5.477	1.47	80	1.90	20	1.30

N=3 Each value represents the mean ± S.D of three experiments

Fig 18

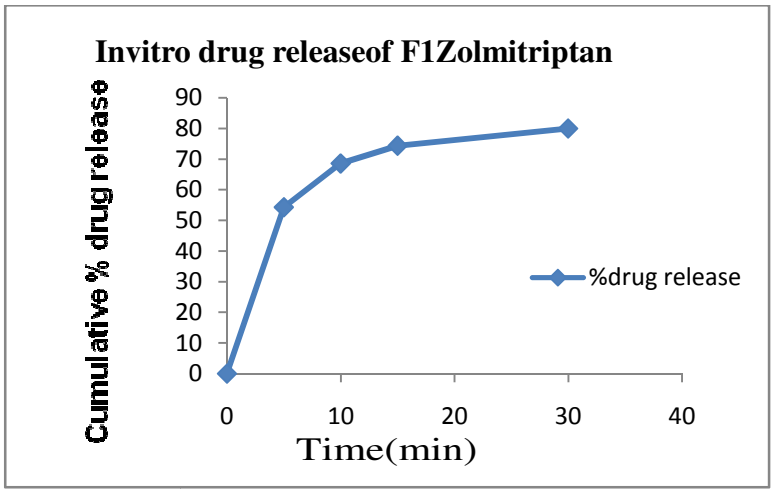

Invitro drug releaseof F1Zolmitriptan
Cumulative % drug release
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
Time(min)
%drug release

Fig: 19

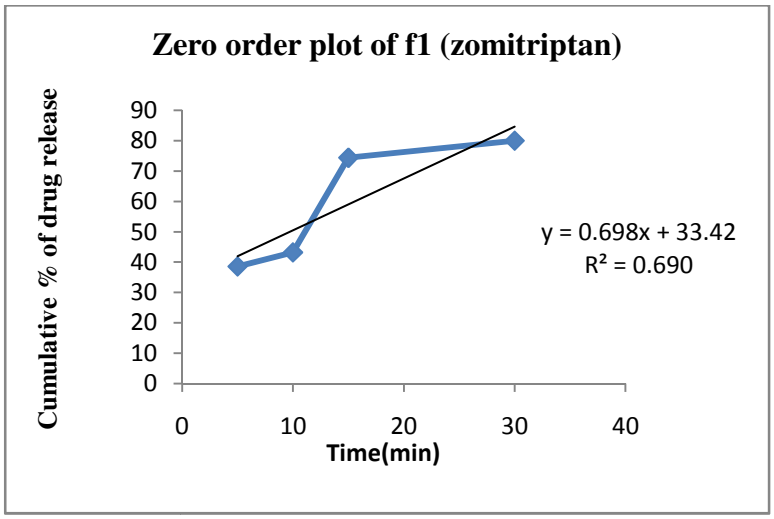

Zero order plot of f1 (zomitriptan)
Cumulative % of drug release
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
Time(min)
y = 0.698x + 33.42
R² = 0.690

Fig: 20

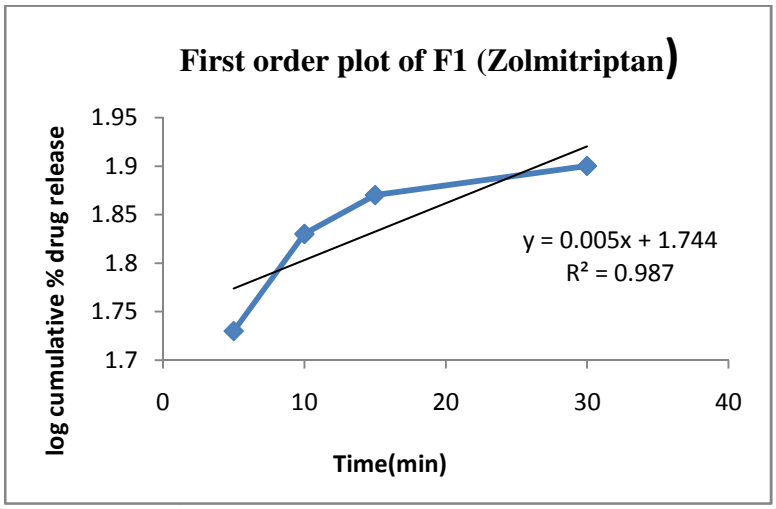

First order plot of F1 (Zolmitriptan)
log cumulative % drug release
1.95
1.9
1.85
1.8
1.75
1.7
0
10
20
30
40
Time(min)
y = 0.005x + 1.744
R² = 0.987

Fig: 21

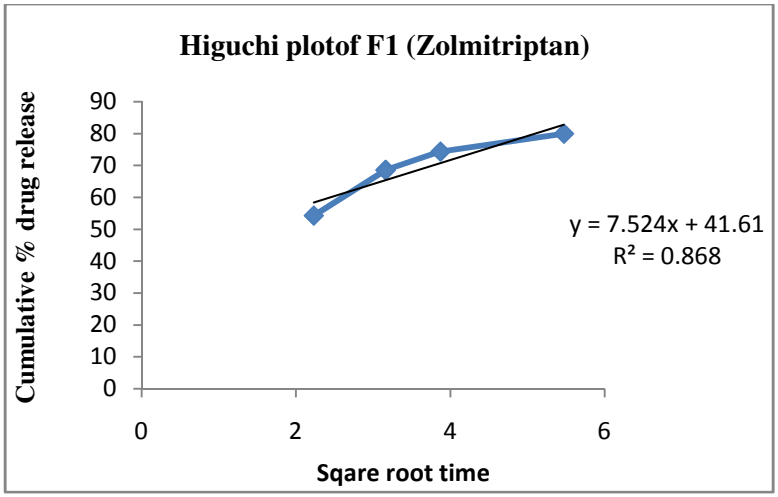


Fig: 22

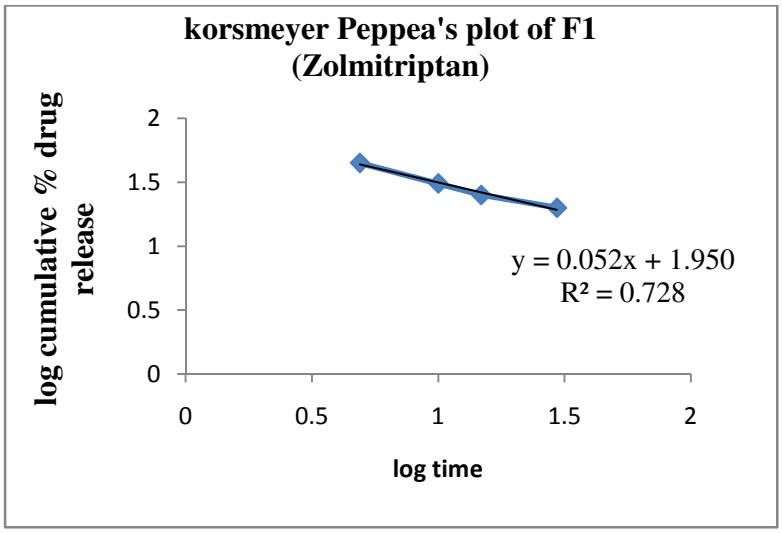


Table: 12 In vitro drug release of (F2) Zolmitriptan

TIME(Min)	Trail 1	Trail 2	Trail 3	Mean	S.D
0	0	0	0	0	0

5	61.8	62.7	64.2	62.9	1.21
10	70.8	71.6	72.2	71.53	0.701
15	73.8	74.7	74.9	74.46	0.585
30	79.9	84.2	84.9	83	2.707

N=3 Each value represents the mean ± S.D of three experiments

Table: 13 Percentage drug release formulation of Zolmitriptan oral disintegrating tablet

Time	**Absorbance**	**Concentration**	**Amount of drug release**	**Amount of drug release mg/500**	**Cummulative drug release**	**% of drug release**
0	0	0	0	0	0	0
5	0.022	0.157	0.003	1.57	1.574	62.98
10	0.025	0.178	0.003	1.78	1.788	71.55
15	0.026	0.185	0.003	1.85	1.860	74.42
30	0.029	0.207	0.004	2.07	2.075	83.02

N=3 Each value represents the mean ± S.D of three experiments

Table 14: Kinetic drug release formulation of Zolmitriptan oral disintegrating tablet

Square root	Log time	% Drug release	log% Drug release	% Drug remaining	log % Drug remaining
2.236	0.698	62.9	1.798	37.1	1.569
3.162	1	71.5	1.854	28.5	1.454
3.872	1.176	74.4	1.871	25.6	1.408
5.477	1.477	83.2	1.920	16.8	1.225

N=3 Each value represents the mean ± S.D of three experiment

Fig: 23

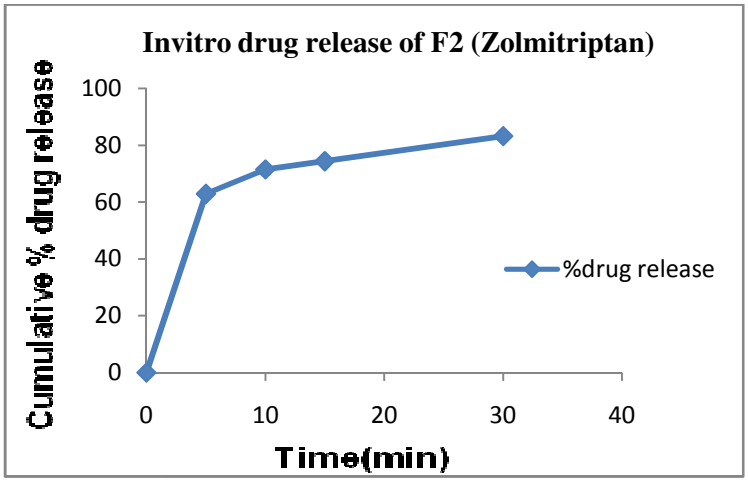


Fig: 24

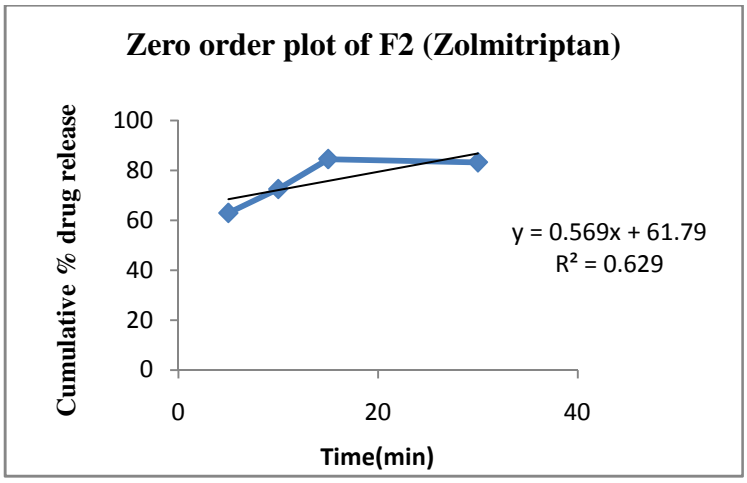


Fig: 25

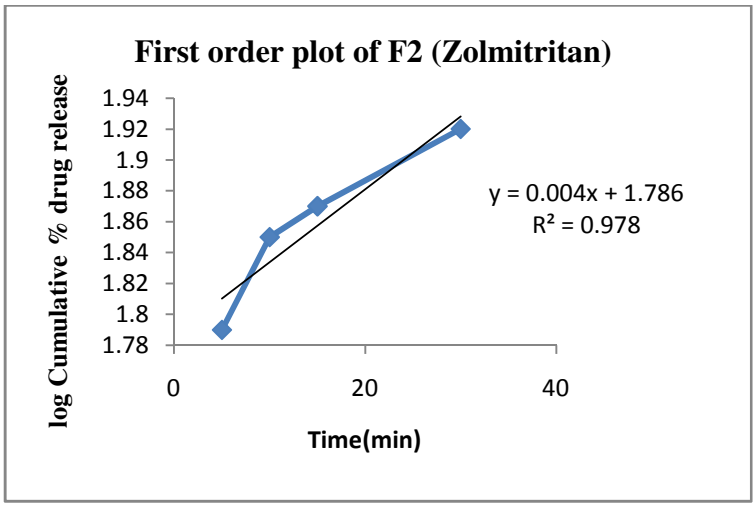


Fig: 26

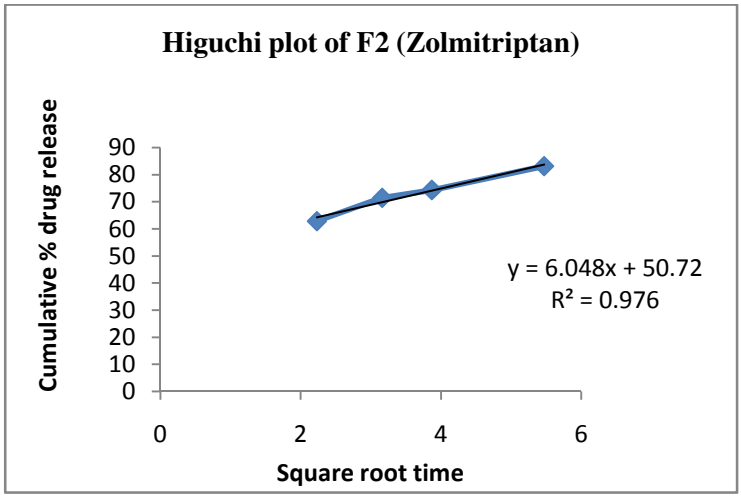


Fig: 27

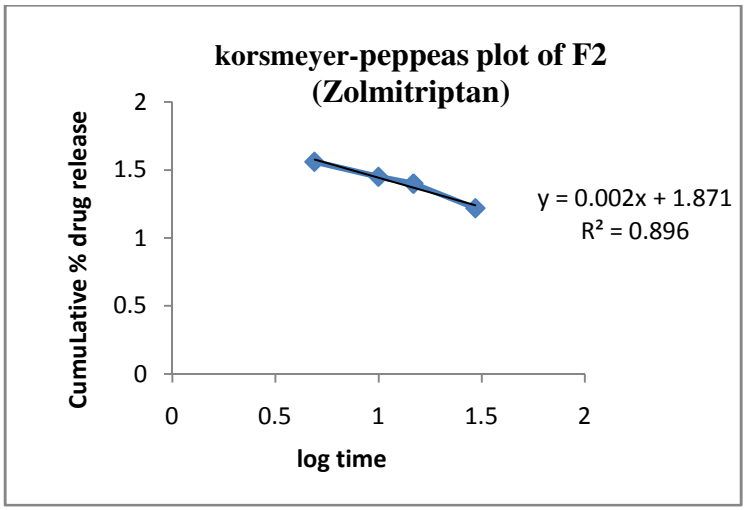


Table: 15 In vitro drug release of (F3) Zolmitriptan

TIME(Min)	Trail 1	Trail 2	Trail 3	Mean	±S.D
0	0	0	0	0	0
5	64.9	65.9	66.7	65.83	0.90
10	70.8	71.6	72.2	71.53	0.70
15	76.5	77.3	77.8	77.2	0.65
30	84.9	85.8	86.7	85.8	0.9

N=3 Each value represents the mean ± S.D of three experiments

Table: 16 Percentage drug release formulation of Zolmitriptan oral disintegrating tablet

Time	Absorbance	Concentration	Amount drug release	Amount of drug release mg/500	Cummulative drug release	% Drug release
0	0	0	0	0	0	0
5	0.023	0.164	0.003	1.642	1.646	65.84
10	0.025	0.178	0.003	1.785	1.789	71.56
15	0.027	0.192	0.003	1.928	1.932	77.28
30	0.03	0.214	0.004	2.142	2.147	85.88

N=3 Each value represents the mean ± S.D of three experiments

Table: 17 Kinetic drug release formulation of Zolmitriptan oral disintegrating tablet

Square root	Log time	% Drug release	log% Drug release	% Drug remaining	log % Drug remaining
2.236	0.698	65.8	1.818	34.2	1.534
3.162	1	71.5	1.854	28.5	1.454
3.872	1.176	77.2	1.887	22.8	1.357
5.477	1.477	85.8	1.933	14.2	1.152

N=3 Each value represents the mean ± S.D of three experiments

Fig: 28

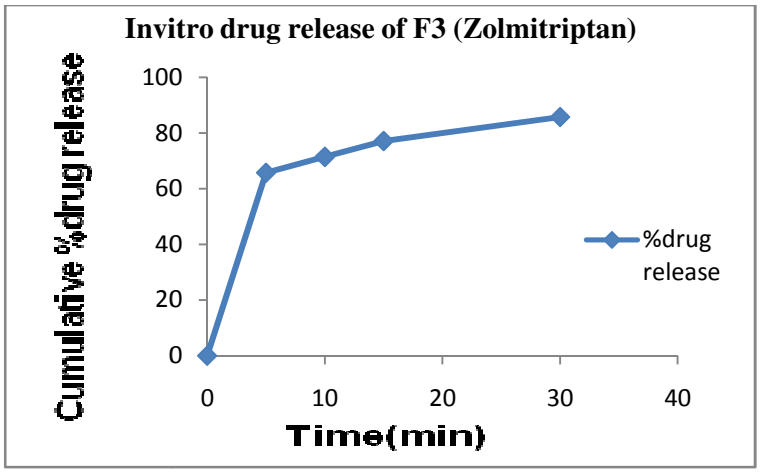


Fig: 29

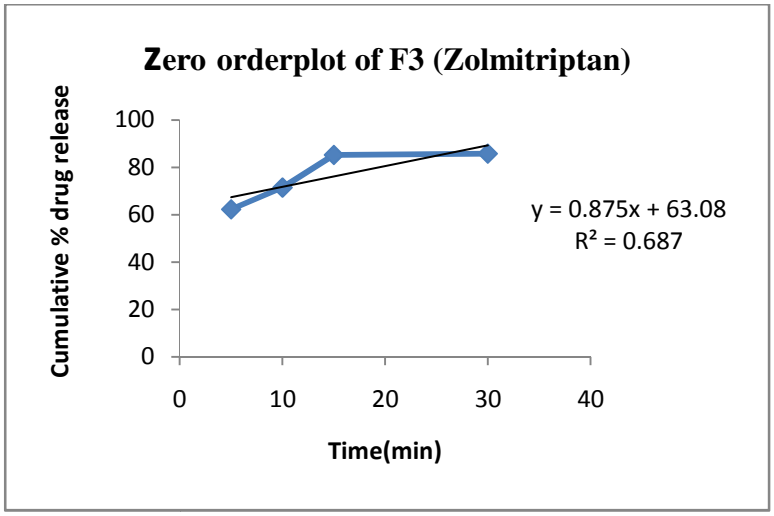


Fig: 30

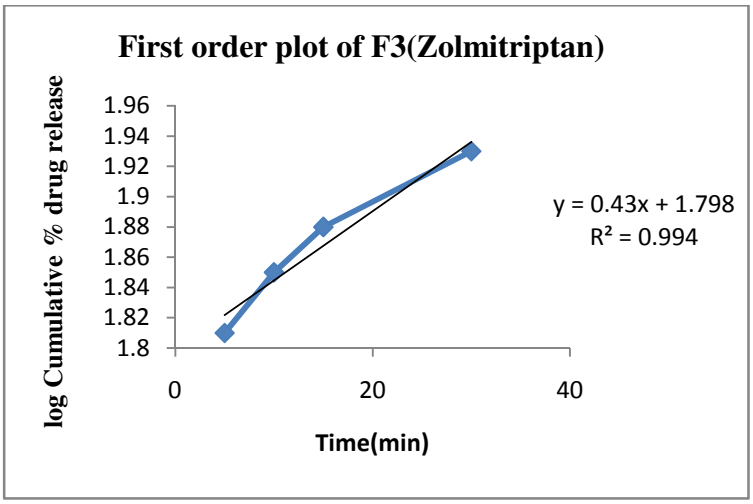

First order plot of F3(Zolmitriptan)
log Cumulative % drug release
1.96
1.94
1.92
1.9
1.88
1.86
1.84
1.82
1.8
0
20
40
Time(min)
y = 0.43x + 1.798
R² = 0.994

Fig: 31

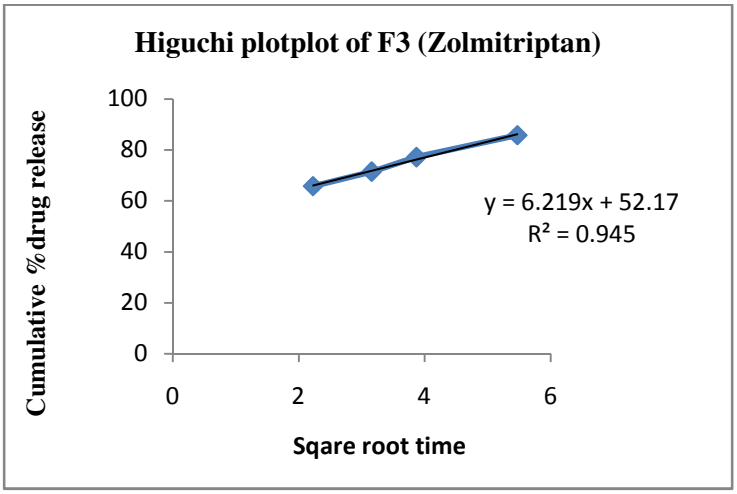

Higuchi plotplot of F3 (Zolmitriptan)
Cumulative %drug release
100
80
60
40
20
0
0
2
4
6
Sqare root time
y = 6.219x + 52.17
R² = 0.945

Fig: 32

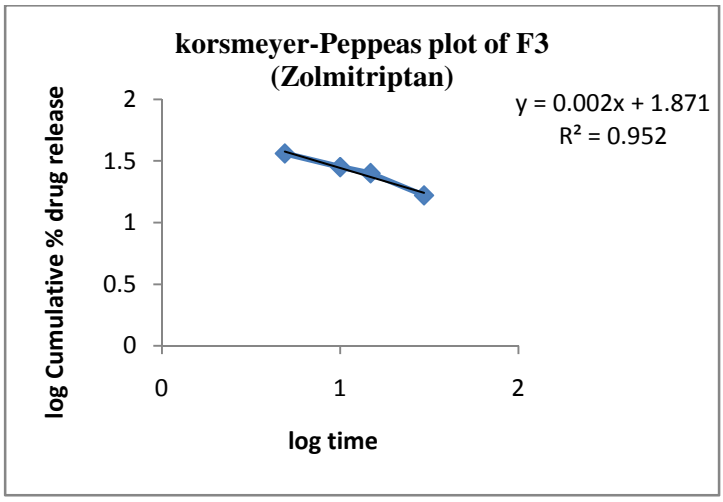


Table: 18 In vitro drug release of (F4) Zolmitriptan

TIME(Min)	Trail 1	Trail 2	Trail 3	Mean	±SD
0	0	0	0	0	0
5	69.8	71.8	72.9	71.5	1.571
10	73.7	74.5	75.1	74.43	0.702
15	78.3	80.1	82.1	80.14	1.900
30	87.5	88.9	89.9	88.60	1.205

N=3 Each value represents the mean ± S.D of three experiments

Table: 19 Percentage drug release formulation of Zolmitriptan oral disintegrating tablet

Time	Absorbance	Concentration	Amount of drug release	Amount of drug release mg/500	Cummulative drug release	% Drug release
0	0	0	0	0	0	0
5	0.025	0.178	0.003	1.785	1.789	71.57
10	0.026	0.185	0.003	1.857	1.860	74.42
15	0.028	0.2	0.004	2	2.003	80.14
30	0.031	0.221	0.004	2.214	2.218	88.6

N=3 Each value represents the mean ± S.D of three experiments

Table: 20 Kinetic drug release formulation of Zolmitriptan oral disintegrating tablet

Square root	Log time	% Drug release	Log% drug release	% Drug remaining	Log % drug remaining
2.236	0.698	27.95	1.446	72.041	1.857
3.162	1	40	1.602	60	1.778
3.872	1.176	47.043	1.672	52.956	1.723
5.477	1.477	88.6	1.947	11.4	1.056

N=3 Each value represents the mean ± S.D of three experiments

Fig: 33

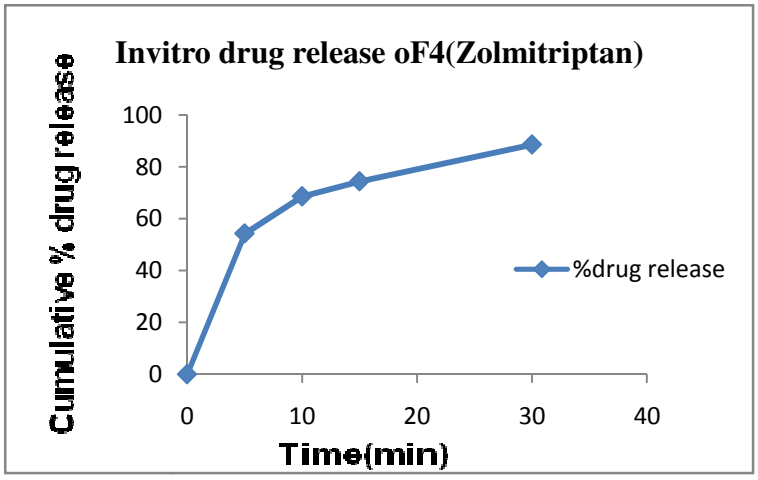


Fig: 34

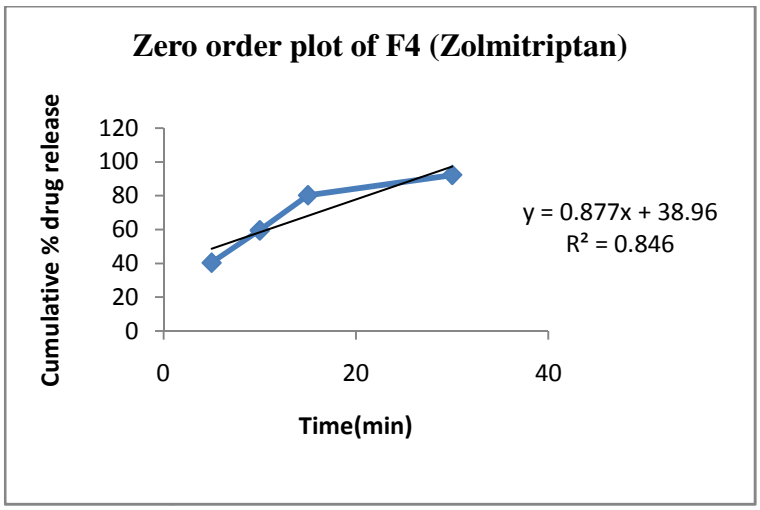


Fig: 35

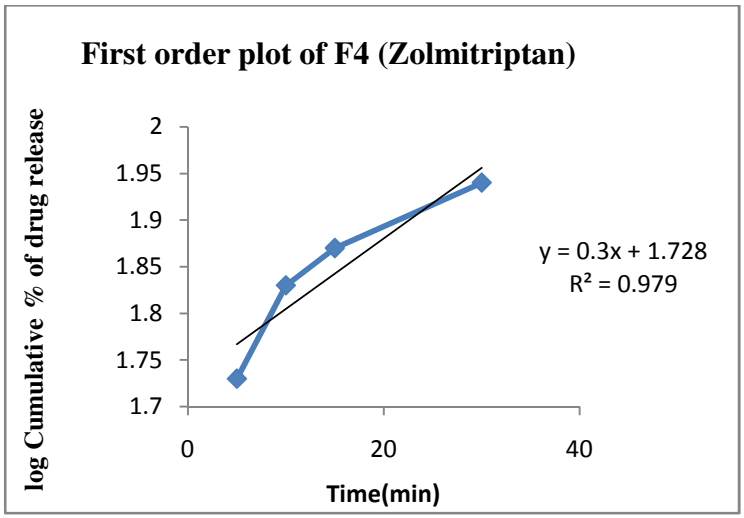

First order plot of F4 (Zolmitriptan)
log Cumulative % of drug release
2
1.95
1.9
1.85
1.8
1.75
1.7
0
20
40
Time(min)
y = 0.3x + 1.728
R² = 0.979

Fig: 36

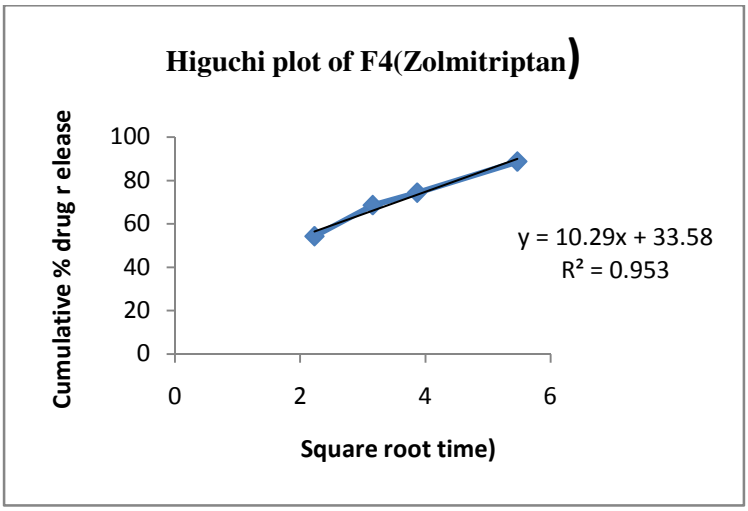

Higuchi plot of F4(Zolmitriptan)
Cumulative % drug r elease
100
80
60
40
20
0
0
2
4
6
Square root time)
y = 10.29x + 33.58
R² = 0.953

Fig: 37

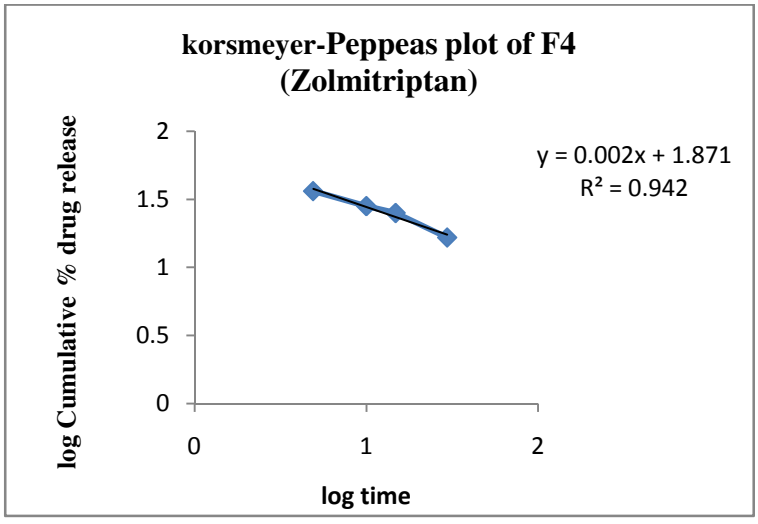

korsmeyer-Peppeas plot of F4
(Zolmitriptan)
log Cumulative % drug release
2
1.5
1
0.5
0
0
1
2
log time
y = 0.002x + 1.871
R² = 0.942

Table: 21 In vitro drug release of (F5) Zolmitriptan

TIME(Min)	Trail 1	Trail 2	Trail 3	Mean	±SD
0	0	0	0	0	0
5	78.3	80.1	82.1	80.16	1.90
10	90	92.1	92.6	91.56	1.379
15	96.5	97.7	97.9	97.3	0.757
30	98.8	98.4	98.9	98.7	0.264

N=3 Each value represents the mean ± S.D of three experiments

Table: 22 Percentage drug release formulation of Zolmitriptan oral disintegrating tablet

Time	Absorbance	Concentration	Amount of drug release	Amount of drug release mg/500	Cummulative drug release	% Drug release
0	0	0	0	0	0	0
5	0.028	0.2	0.004	2	2.004	80.16
10	0.032	0.228	0.004	2.285	2.289	91.58
15	0.034	0.242	0.004	2.428	2.433	97.32
30	0.034	0.246	0.004	2.464	2.469	98.76

N=3 Each value represents the mean ± S.D of three experiments

Table: 23 Kinetic drug release formulation of Zolmitriptan oral disintegrating tablet

Square root	Log time	% Drug release	Log% drug release	% Drug remaining	log % Drug remaining
2.236	0.698	80.1	1.903	19.9	1.298
3.162	1	91.5	1.961	8.5	0.929
3.872	1.176	97.3	1.988	2.7	0.431
5.477	1.477	98.7	1.994	1.3	0.113

N=3 Each value represents the mean ± S.D of three experiments

Fig: 38

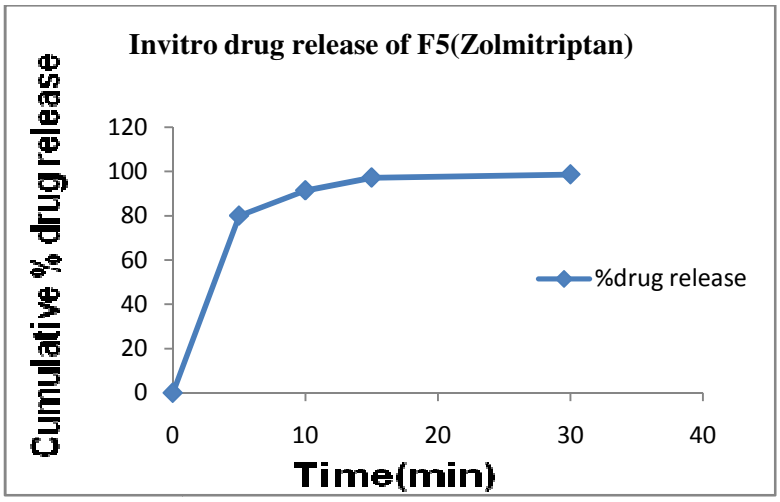

Invitro drug release of F5(Zolmitriptan)
Cumulative % drug release
120
100
80
60
40
20
0
0
10
20
30
40
Time(min)
%drug release

Fig: 39

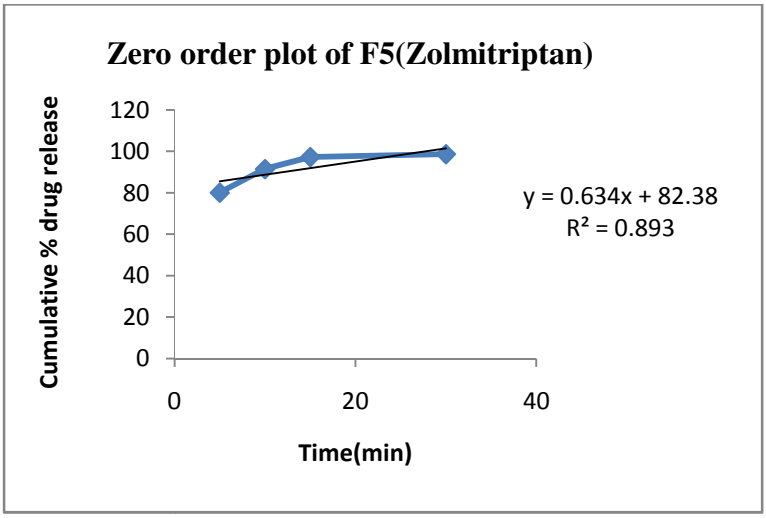

Zero order plot of F5(Zolmitriptan)
Cumulative % drug release
120
100
80
60
40
20
0
0
20
40
Time(min)
y = 0.634x + 82.38
R² = 0.893

Fig: 40

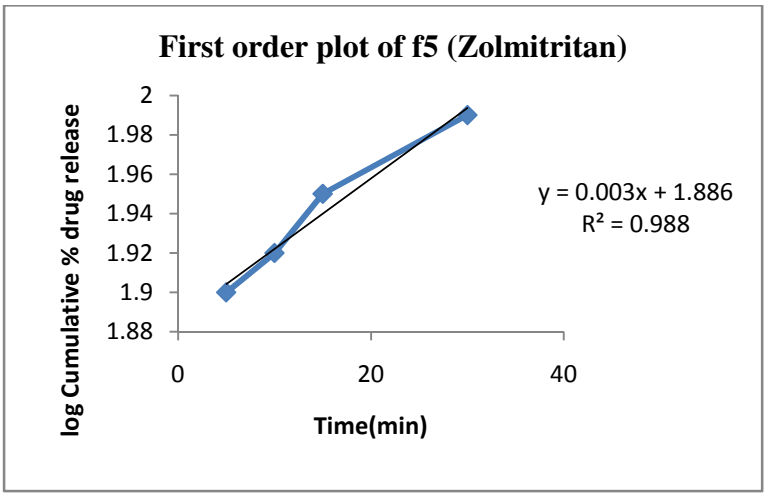

First order plot of f5 (Zolmitritan)
log Cumulative % drug release
2
1.98
1.96
1.94
1.92
1.9
1.88
0
20
40
Time(min)
y = 0.003x + 1.886
R² = 0.988

Fig: 41

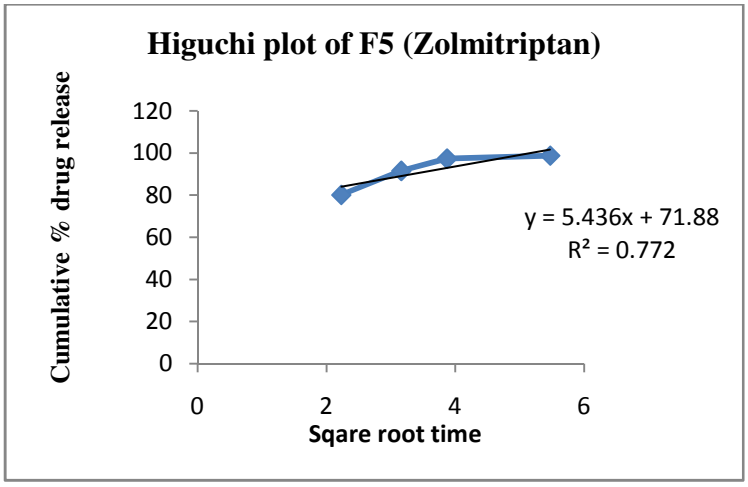

Higuchi plot of F5 (Zolmitriptan)
Cumulative % drug release
120
100
80
60
40
20
0
0
2
4
6
Sqare root time
y = 5.436x + 71.88
R² = 0.772

Fig: 42

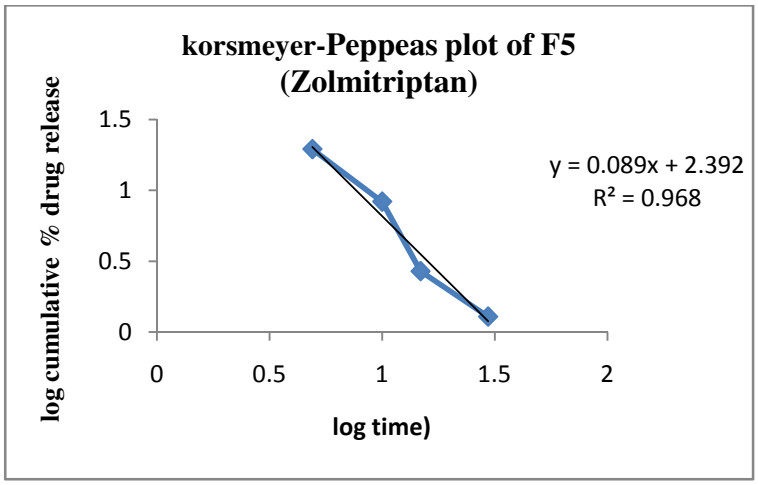


Table: 24 In vitro drug release of (F6) Zolmitriptan

TIME(Min)	Trail 1	Trail 2	Trail 3	Mean	±SD
0	0	0	0	0	0
5	81.6	83.4	84.2	83.06	1.33
10	92.8	94.8	95.6	94.4	1.44
15	96.5	97.7	97.9	97.36	0.75
30	98.8	98.2	99.8	99.06	1.02

N=3 Each value represents the mean ± S.D of three experiments

Table: 25 Percentage drug release formulation of Zolmitriptan oral disintegrating tablet

Time	Absorbance	Concentration	Amount of drug release	Amount of drug release mg/500	Cummulative drug release	% Drug release
0	0	0	0	0	0	0
5	0.029	0.207	0.004	2.071	2.075	83.02
10	0.033	0.235	0.004	2.357	2.361	94.45
15	0.034	0.242	0.004	2.428	2.433	97.33
30	0.035	0.25	0.005	2.5	2.505	99

N=3 Each value represents the mean ± S.D of three experiments

Table: 26 Kinetic drug release formulation of Zolmitriptan oral disintegrating tablet

Square root	Log time	% Drug release	Log% drug release	% Drug remaining	log % Drug remaining
2.236	0.698	83	1.919	17	1.230
3.162	1	94.4	1.974	5.6	0.748
3.872	1.176	97.3	1.988	2.7	0.431
5.477	1.477	99	1.995	1	0

Each value represents the mean ± S.D of three experiments

Fig: 43

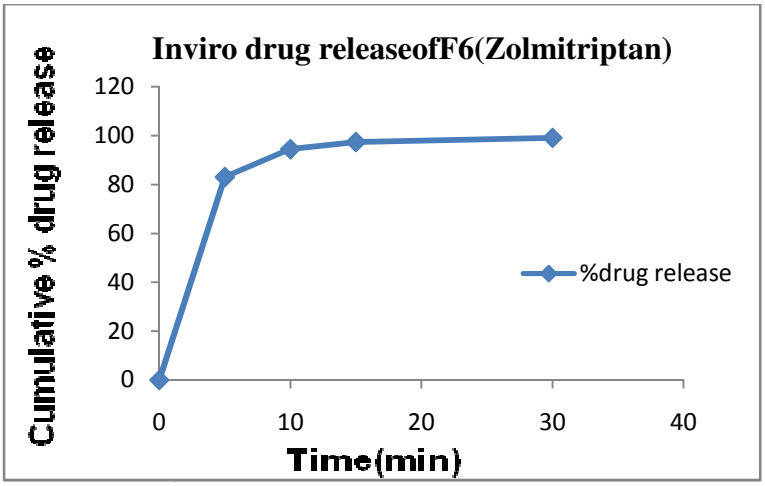


Fig: 44

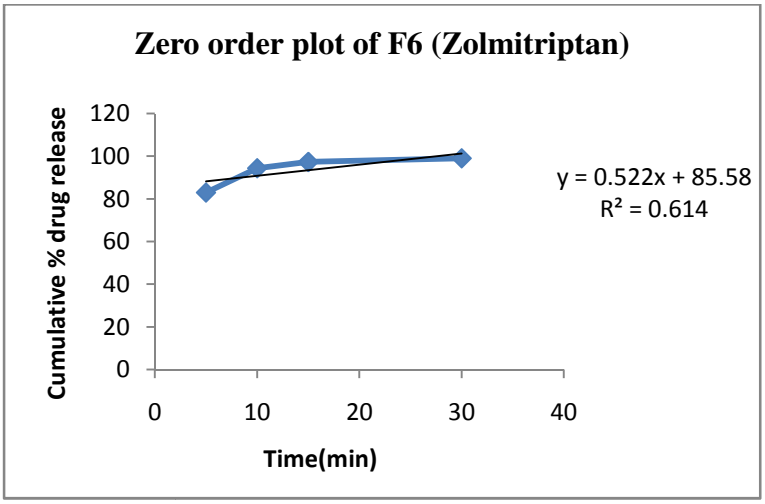


Fig: 45

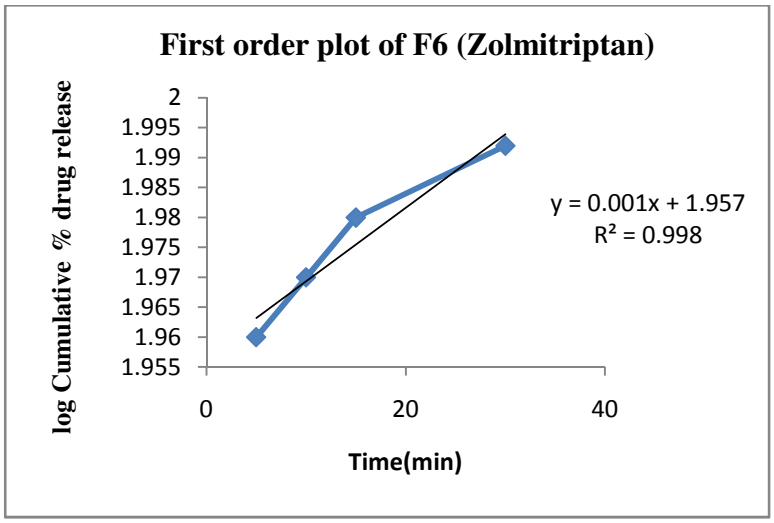

First order plot of F6 (Zolmitriptan)
log Cumulative % drug release
2
1.995
1.99
1.985
1.98
1.975
1.97
1.965
1.96
1.955
0
20
40
Time(min)
y = 0.001x + 1.957
R² = 0.998

Fig: 46

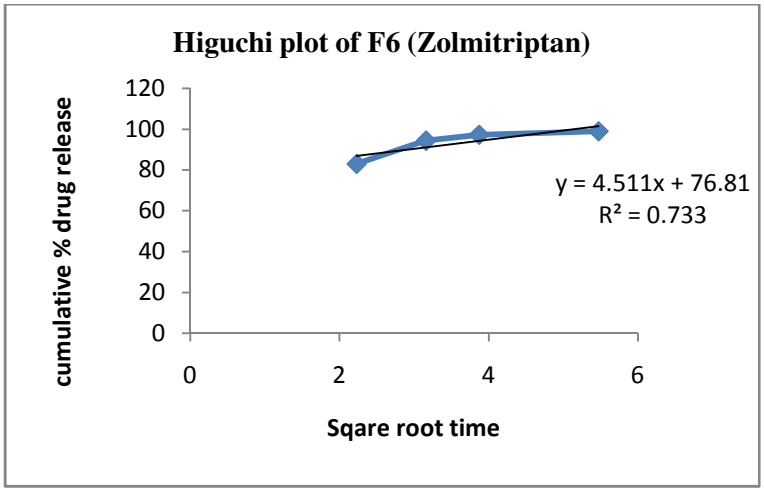

Higuchi plot of F6 (Zolmitriptan)
cumulative % drug release
120
100
80
60
40
20
0
0
2
4
6
Sqare root time
y = 4.511x + 76.81
R² = 0.733

Fig: 47

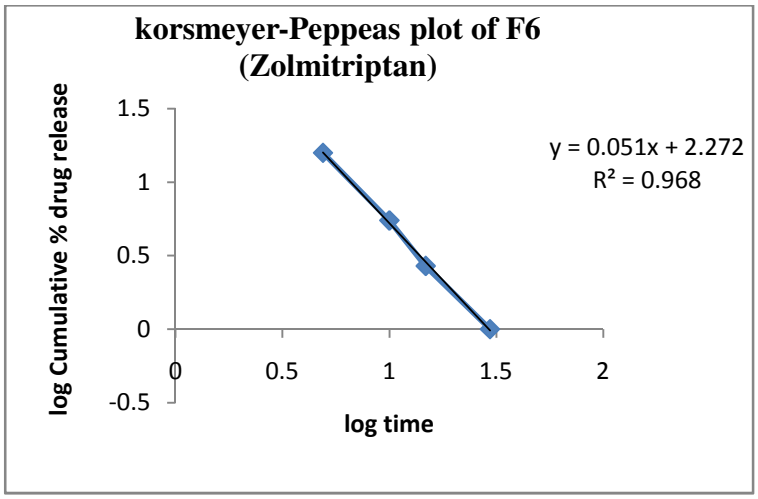


Table: 27 COMPARATIVE STUDY OF INVITRO % DRUG RELEASE PROFILE OF ZOLMITRIPTAN ORAL DISINTEGRATING TABLETS:

TIME	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	54.36	62.9	66.7	71.5	80.16	83.06
10	68.6	71.53	72.2	74.43	91.56	94.4
15	73.86	74.46	77.8	80.14	97.3	97.36
30	80.16	83	86.7	88.6	98.7	99.06

Fig: 48

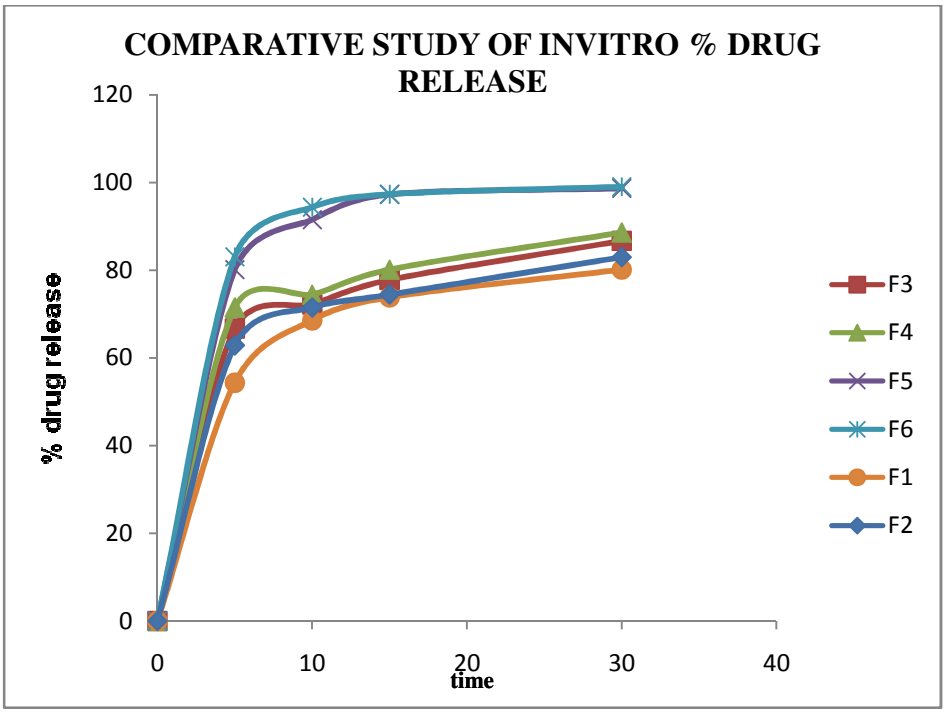


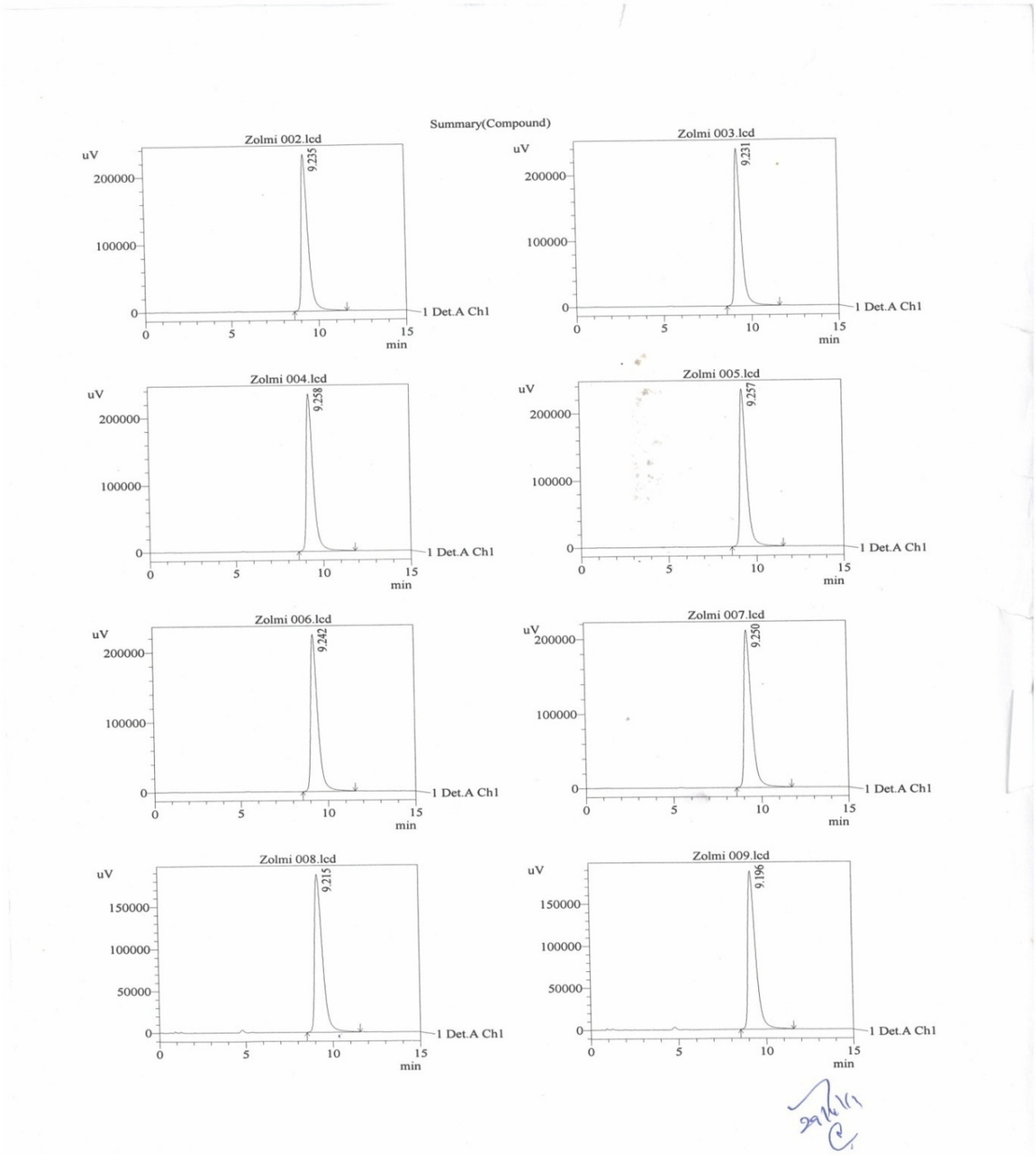
TABLE: 28 Kinetic Values Obtained from Different Plot of Formulation (F_1To F6)

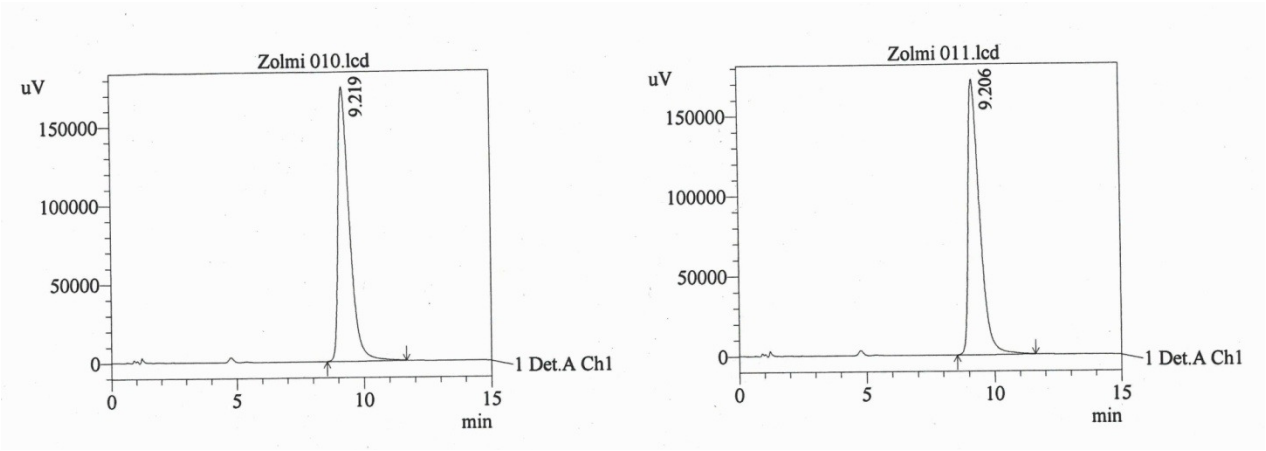
Formulation Code	Zero order plot	First order plot	Higuchi's plot	Korsemeyer peppas plot		Possible mechanism of drug release
	R^2	R^2	R^2	R^2	n	

F1	0.690	0.728	0.868	0.987	0.052	Fickian release
F2	0.629	0.896	0.976	0.972	0.002	Fickian release
F3	0.687	0.953	0.994	0.95	0.063	Fickian release
F4	0.846	0.969	0.979	0.945	0.065	Fickian release
F5	0.893	0.988	0.772	0.968	0.089	Fickian release
F6	0.614	0.998	0.733	0.998	0.051	Fickian release

DRUG CONTENT ESTIMATION OF ZOLMITRIPTAN FORMULATION [54]

Fig: 49 Chromatograms of Zolmitriptan Oral disintegration tablet





<< Detector A >>

ID#1 Compound Name: Zolmitriptan

Peak#	Ret. Time	Area	Area %	Tailing Factor	eoretical Plat
1	9.235	6192129	100.000	1.559	3107.514
1	9.231	6202065	100.000	1.567	3300.330
1	9.258	6217339	100.000	1.539	3162.955
1	9.257	6198350	100.000	1.549	3174.543
1	9.242	6197642	100.000	1.518	2880.298
1	9.250	6265651	100.000	1.523	2468.763
1	9.215	5748518	100.000	1.529	2257.218
1	9.196	5742308	100.000	1.606	2256.928
1	9.219	5443847	100.000	1.599	2162.337
1	9.206	5413525	100.000	1.624	2116.893
	9.231	5962137	100.000	1.561	2688.778
	0.234	5.708	0.000	2.384	17.846
	9.258	6265651	100.000	1.624	3300.330
	9.196	5413525	100.000	1.518	2116.893
	0.022	340348	0.000	0.037	479.834

Table: 29

TABLE: 30 Assay of formulation (F6) Zolmitriptan oral disintegrating tablets

S.No	Standard	Test A1	TestA2
1	6192129	5932532	5907691
2	6202065	5941328	5915152
3	6217339		
4	6198350		
5	6197642		
6	6265651		
Average	6212196	5936930	5911422
S.D	27541.75	6219.71	5275.72
%RSD	0.44	0.10	0.09
%Assay		95.92	95.99
Drug content(mg)		2.430057	2.419616

Assay

=Test area/std area*50/50*5/50*100/393.2*100/2.5*99.16

Drug

content = Test area/std area*50/50*5/50*100/393.2*99.98/100*100

9. DISCUSSION

Zolmitriptan is a serotonin receptor agonist used in the acute treatment of migraine attacks Conventional Zolmitriptan not suitable where quick onset of action is required. To overcome these problems, there is a need to develop oral disintegrating dosage form, particularly one that would rapidly disintegrate in saliva and could be administered without water anywhere anytime.

The oral disintegrating tablets of Zomitriptan were prepared by direct compression superdisintegrants addition method using Sodium starch glycolate, Crospovidone and Croscarmellose sodium in different concentrations. There are total six formulations (F1 to F6) were prepared and evaluated for Weight variation, Thickness, Friability, Hardness, Disintegration time, and dissolution study.

Results of all formulations showed the drug release rate was increased when the super disintegrants were used in combination and alone. . The Weight variation, Friability, Hardness and drug content were found to be within the limit and no significant variation. The Disintegration time for F1-F6 formulations was found to be 10 to 30 seconds. Based on the In-vitro dissolution percentage% of drug release of the formulation F1-F6 shows(80.16%-99.06%) .The formulation f6 showed maximum drug release within 10 minutes (94.4%) and F6 containing Crosspovidone as a superdisintegrant showed minimum disintegration time 15 seconds. The results shows the disintegration time was increased in the following manner.

Crosspovidone > Crosscarmellose sodium > sodium starch glycolate.

Based on the results the best formulation (F6) shows the drug content 95.9%.

In all the f1-f6 formulation are subjected to the release kinetics. In the kinetic results shows, best fit in first order drug release and followed by the ‘n’ value shows between (0.002-0.089), follows Fickian’s release mechanism

10. CONCLUSION

The oral disintegrating tablets of Zolmitriptan were prepared by using different super disintegrants in different ratios. Based on the study concluded that the F6 formulation by using Zolmitriptan and superdisintegrants Crosspovidone shows maximum drug content and invitro percentage drug release, and faster disintegration time.

And all the formulations shows first order release kinetics and best fit into Fickian's release mechanism.

10. REFERENCES

1. Bhupendra G, Prajapati, Bhaskar Patel., International Journal of PharmTech Research,Vol.2, No.3, pp 1893-1899
2. J.Ramesh, Dr.V.Prabhakar Reddy, Dr.G.chandrasekhar Rao., int.j.ph.sci.,may-aug, 2010;2(2):488-495.
3. Jaysukh J Hirani, Dhaval A Rathod, Kantilal R Vadalia., Tropical Journal of Pharmaceutical Research., April 2009; 8 (2): 161-172.
4. Manoj Ashok Wagh, Kothawade Parag Dilip, Kishor Sahebrao Salunkhe, Nayana Vijay Chavan, Vandana Radheshyam Daga., International Journal of Drug Delivery 2 (2010) 98-107
5. Rakesh Pahwa, Mona Piplani, Prabodh C. Sharma, Dhirender Kaushik and Sanju Nanda Der Pharmacia Lettre., 2010, 2 (2): 35-48.
6. Prameela rani,n. Archana, p. Siva teja, p. Mohan vikas, m. Sudheer kumar. C. Bala sekaran., International Journal of Applied Pharmaceutics Vol 2, Issue 3, 2010.
7. Brown D, Orally disintegrating tablets: Taste over speed. Drug Deliv Tech, 2001; 3(6): 58-61.
8. US Food and Drug Administration, CDER Data Standards Manual. 2003., http://www.fda.gov/ cder/dsm/DRG/drg00201.htm.,Accessed 6 February 2007.
9. Tablets. European Pharmacopoeia.Ed. 4, Supplement 4.2; 2002. p2435.
10. Debjit Bhowmik, fast Dissolving tablets: An overview Journal of chemical and pharmaceutical research , 2009:1(1) :163-177.
11. Journal of Applied Pharmaceutical Science 01 (04); 2011: 35-45
12. Reddy LH, Ghosh B, and Rajneesh., Fast dissolving drug delivery systems: a review of the literature. Indian J. Pharm. Sci 2002; 64(4): 331-336.
13. Dobetti L., Fast melting tablets: Development and technologies. Pharm Technol N Am 2001; 44-50.
14. Kizumi K, Watanabe Y, Morita K, et al., New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor: A sublimating material. Int J Pharm 1997; 152: 127-131.

15. Makino T, Yamada M and Kikuta J. Fast dissolving tablet and its production, European Patent 0553777 A2 1993. Reddy LH, Ghosh B, and Rajneesh., Fast dissolving drug delivery systems: a review of the literature. Indian J. Pharm. Sci 2002; 64(4): 331-336.

16. Kuno Y, Kojima M, Ando S, et al., Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. J Control Release 2005; 105: 16-22.

17. Augsburger LL, Brzeczko AW, Shah U. Encyclopedia of Pharmaceutical Technology. 2nd edition.2002; 3, 2623-2638.

18. Augsburger LL, Brzeczko AW, Shah U. Encyclopedia of Pharmaceutical Technology. 2nd edition.2002; 3, 2623-2638.

19. Bagul US. 2006; 4(4). Available at http ://www.pharmainfo.net/reviews/current-status tablet- disintegrants-review Accessed on 18 Oct. 2009.

20. Camarco W, Ray D, Druffner A. Pharma Tech. 2006;http:// pharmtech., Find Pharma.com.Superdisintegrants for Orally Disintegrants /Article Standard/ Article/detail/378398. Accessed on 19 nov2009.

21. SharmaS.Pharmainfo.net, 2008;6(5).Available at http://www.pharmainfo.net/reviews/ orodispersable-tablet-review Accessed on 22 Oct. 2009.

22. Washburn EW. Phys Rev. 1921; 17, 273-283.

23. A.A. Kalanuria[1] and B.L. Peterlin. Clinical Medicine Insights. Journal Analytics Clinical Medicine: Therapeutics. 2009; vol -1; 397–413.

24. Gilmore, Benjamin ,Michae, Magdalena. American Family Physician. Vol. 83; Issue 3; Feb 2011.

25. Vollono C[1], Vigevano F, Tarantino S, Valeriani M. Triptans other than sumatriptan in child and adolescent migraine: literature review. 2011 Mar;11(3):395-401. doi: 10.1586/ern. 10.147.

26. Eiland, Lea S; Hunt, Melissa O. The use of triptans for pediatric migraines. Paediatric Drugs. Dec 2010; Vol. 12; Issue 6.

27. Johnston, Mollie M; Rapoport, Alan M. Triptans for the management of migraine. Drugs Aug 2010; Vol. 70; Issue 12.

28. Francis, George J; Becker, Werner J; Pringsheim, Tamara M. Acute and preventive pharmacologic treatment of cluster headache. Neurology. Aug 2010; Vol. 75; Issue 5.

29. Majumdar, A; Ahmed, M A S; Benton, S. Cluster headache in children--experience from a specialist headache clinic. European journal of Paediatric Neurology : ejpn : official journal of the european paediatric neurology society Nov 2009; Vol. 13; Issue 6.

30. Fotuhi, Majid; Glaun, Braeme; Quan, Susan Y; Sofare, Tzipora. Vestibular migraine: a critical review of treatment trials. Journal of neurology May 2009; Vol. 256; Issue 5.

31. Tyagi, Alok; Matharu, Manjit. Evidence base for the medical treatments used in cluster headache. Current pain and headache reports. Apr 2009; Vol. 13; Issue 2**.**

32. Silver, Shawna; Gano, Dawn; Gerretsen, Philip. Acute treatment of paediatric migraine: a meta-analysis of efficacy. Journal of paediatrics and child health. Jan 2008; Vol. 44; Issue 1-2.

33. Peterlin, B Lee; Rapoport, Alan M. Clinical pharmacology of the serotonin receptor agonist, zolmitriptan. Expert opinion on drug metabolism & toxicology. Dec 2007; Vol. 3; Issue 6.

34. Sternieri, Emilio; Coccia, Ciro Pio Rosario; Pinetti, Diego; Ferrari, Anna. Pharmacokinetics and interactions of headache medications, part I: introduction, pharmacokinetics, metabolism and acute treatments. Expert opinion on drug metabolism & toxicology. Dec 2006; Vol. 2; Issue 6.

35. Dowson, Andrew J; Almqvist, Per. Part III: The convenience of, and patient preference for, zolmitriptan orally disintegrating tablet. Current medical research and opinion 2005; vol. 21; suppl 3.

36. Tepper, Stewart J; Millson, David. Safety profile of the triptans. expert opinion on drug safety. Mar 2003; Vol. 2; Issue 2**,**

37. Villalón, Carlos M; Centurión, David; Valdivia, Luis Felipe; de Vries, Peter; Saxena, Pramod R. Migraine: pathophysiology, pharmacology, treatment and future trends. Current vascular pharmacology. Mar 2003; Vol. 1; Issue 1.

38. Dowson, Andrew J; Charlesworth, Bruce. Review of zolmitriptan and its clinical applications in migraine. Expert opinion on pharmacotherapy. Jul 2002; Vol. 3; Issue 7.

39. Adelman, J U; Lewit, E J. Comparative aspects of triptans in treating migraine. Clinical cornerstone. 2001; Vol. 4; Issue 3.

40. Tfelt-Hansen, P; De Vries, P; Saxena, P R. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. DRUGS. Dec 2000; Vol. 60; Issue 6

41. Egilius L H Spierings, Alan M Rapoport, David W Dodick, Bruce Charlesworth Brigham and Women's Hospital, Boston, Massachusetts 02481-2106, USA. CNS Drugs. 02/2004; 18(15):1133-41.

42. Ch. Anil kumar Y.Ganesh Kumar D.Satyavati , B.Swetha , D.Narasimha Rao formulation and evaluation of rapid disintegrating tablets of zolmitriptan-using different superdisintegrants; ISSN 2278 – 4357 volume 2, issue 6, 5206-5217.

43. Andrew J. Dowson, Michael Bundy, Rebecca Salt, Shaun G. Kilminster Headache Care 09/2006; Patient preference for different formulations of zolmitriptan: results of two prospective studies 3(2-3):73-81.

44. Diener HC, Evers S, Gendolla S AInt J Clin Pract.,The therapeutic profile of zolmitriptan in clinical practice. 2004 Aug; 58 (8): 795-800.

45. ZOMIG ZMT- zolmitriptan tablet, orally disintegrating., AstraZeneca Pharmaceuticals LP AstraZeneca 2007, 2008Wilmington, DE 19850.,Rev 10/08 SIC 30086–06

46. Handbook of pharmaceutical excipients, Raymond C Rowe.6thedition.Pg No:424,185,208,206,663.

47. Handbook of pharmaceutical excipients, Raymond C Rowe .6^{h}edition.Pg No:701,404,667.

48. Citric acid From Wikipedia, the free encyclopedia ″E330" redirects here. For the locomotive, see FS Class E330.)

49. Pharmacological Action\(CID 311 from Pub Chem.

50. N. Hazee Peera, D. Lohithasu, S. K. Sahoo1, M. Santhosh Naidu, K. Mani Kumar1 and V. Anil Kumar2., Formulation development and evaluation of oral disintegrating tablets of Zolmitriptan, Der Pharmacia Lettre, 2013, 5 (2):324-332.

51. Guidance for Industry Orally Disintegrating Tablets,U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) ,December 2008:1-7.

52. Gowtham Kumar, Dokala, CH. Pallavi. International Journal of Research in Pharmaceutical and Biomedical Sciences, Jan– Mar 2013:Vol. 4 (1) : 155-158.

53. Tentu nageswara rao ,T.parvathamma and T.B patrudu. estimation of zolmitriptan by a new rp-hplc method., Department of analytical chemistry, international institute of bio technology and toxicology.(IIBAT),Padappai-601301,Kanchipuram(DT), Tamilnadu, india. department of engineering chemistry GITAM university, Hyderabad campus.

54. Raghavendra Rao, Syeda Humaira, Mangesh R. Munde, International Journal of Biomedical and Advance Research. 2010, validated Uv spectroscopic method for estimation of zolmitriptan from tablet formulations, Full-Text , DOI: 10.7439/ijbar.v1i3.5.

55. Korsmeyer R.W, gurny, R.peppas, mechanism of solute release from porous hydrophilic polymers,international journal of pharmaceutical science.1983;25-35.

56. Higuchi T., mechanism of sustained action medication: theoretical analysis of rate of release of solid drug dispersed in solid matrix. journal of pharmaceutical sciences.1963;1145-1149.